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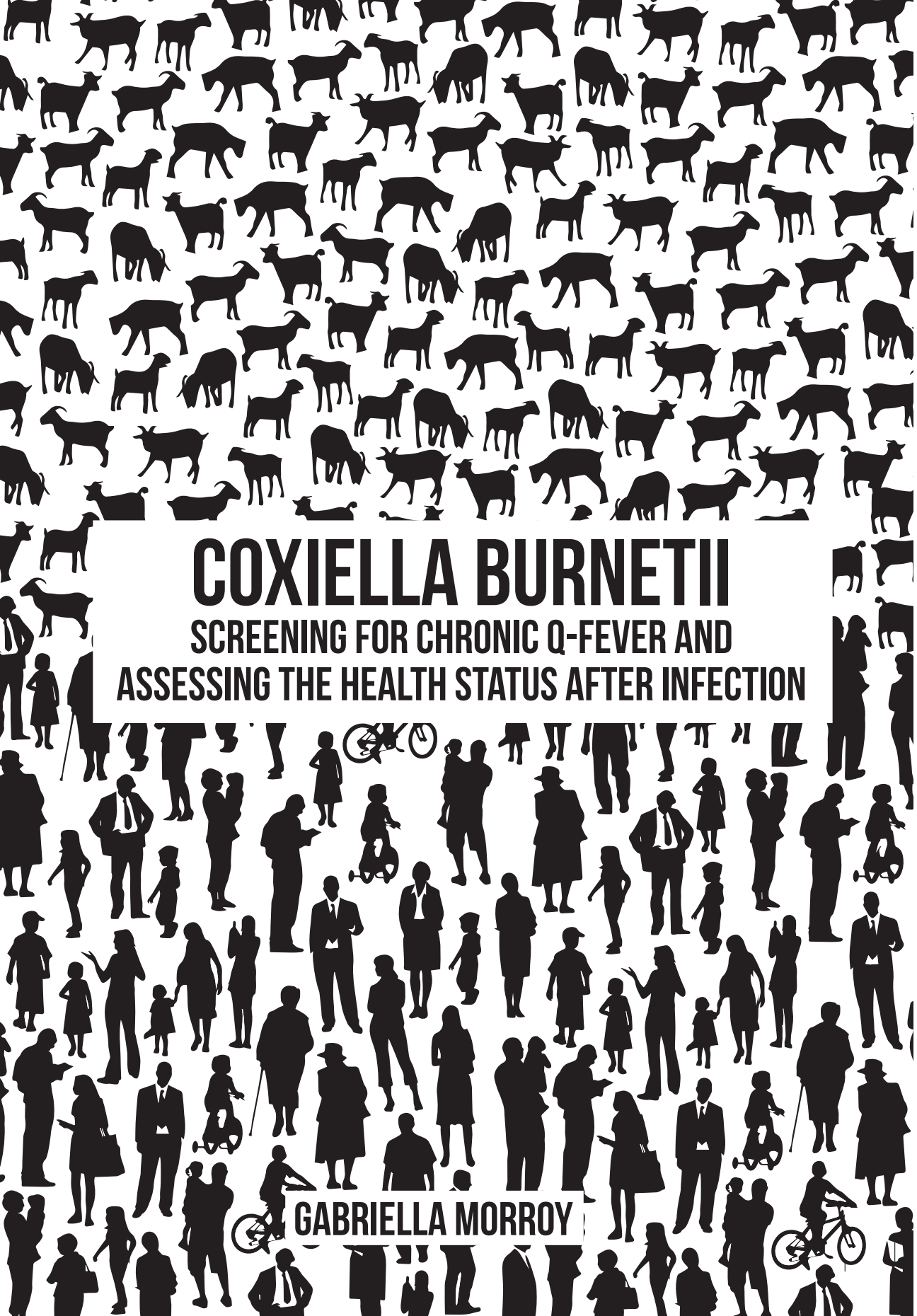

COXIELLA BURNETII

SCREENING FOR CHRONIC Q-FEVER AND ASSESSING THE HEALTH STATUS AFTER INFECTION

GABRIELLA MORROY

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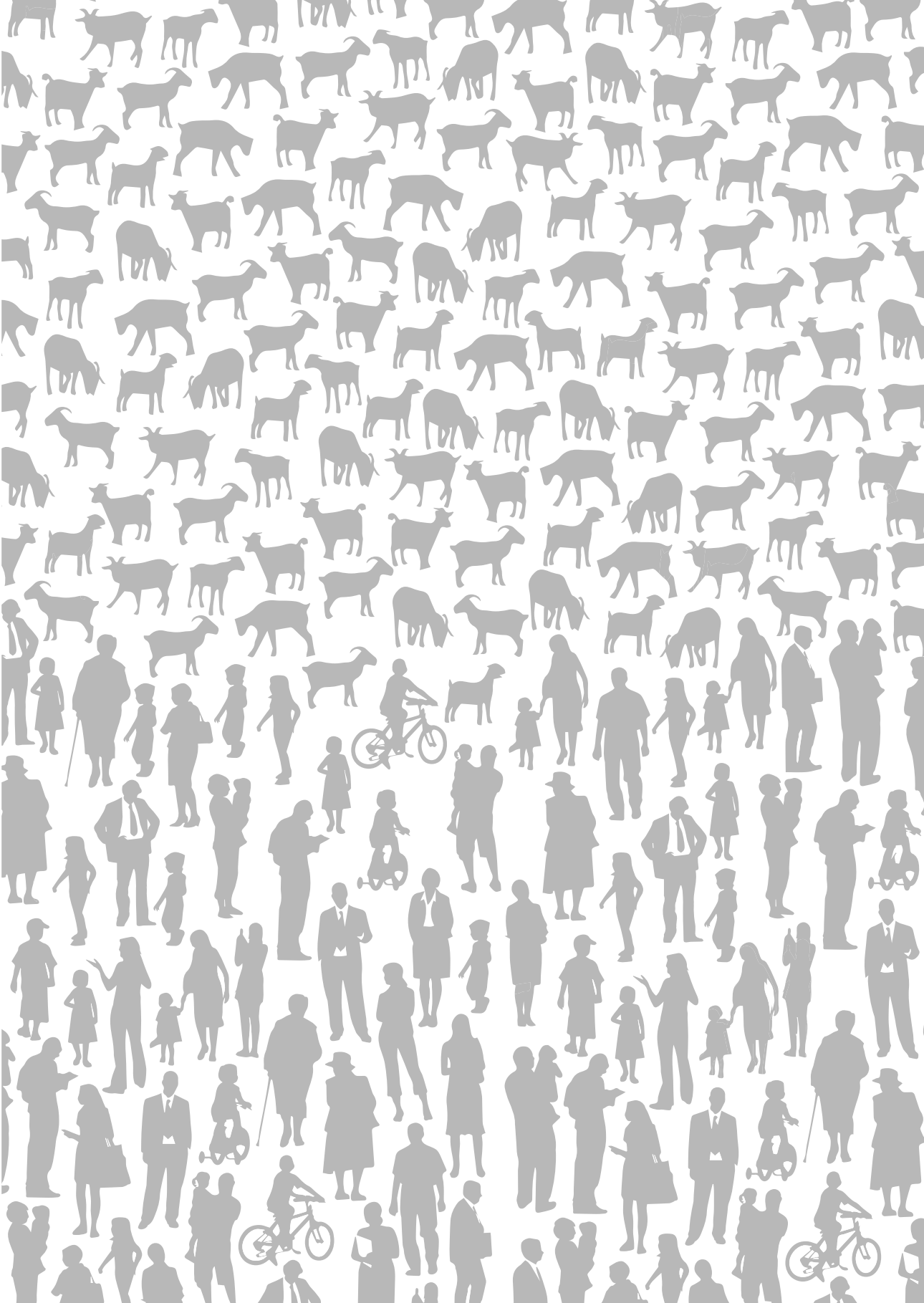

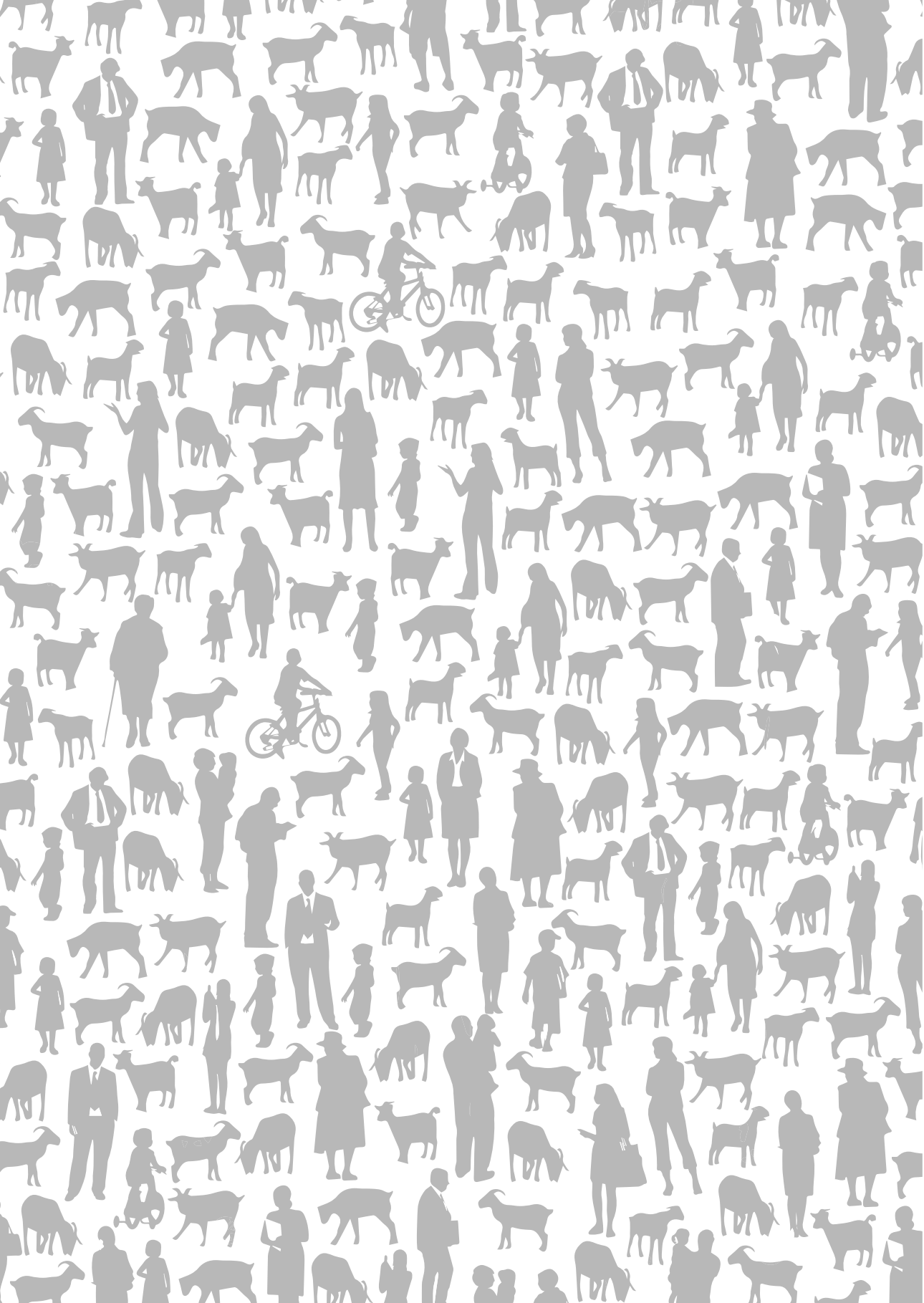

Chapter 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

This thesis comprises studies on two important health problems that people may experience in the aftermath of the large Q-fever epidemic in the Netherlands: chronic Q-fever and persistent fatigue after a *Coxiella burnetii* (*C. burnetii*) infection. These studies are described from a public health perspective.

It is well established that screening for IgG antibodies against phase I of *C. burnetii* is the main strategy for early detection of chronic Q-fever. However, there are important unanswered questions that are addressed in this thesis:

1. What serological follow-up did Q-fever patients in part of Noord Brabant receive?
2. What is the best screening regimen for timely identification of chronic Q-fever?
3. Is screening of the general population for chronic Q-fever years after a Q-fever outbreak useful?

In contrast to chronic Q-fever, persisting fatigue after acute Q-fever, also referred to as the Q-fever Fatigue Syndrome (QFS), is not a life threatening condition. As post infectious fatigue affects a large proportion of Q-fever patients it is an important public health problem. The following questions pertain to an impaired health status, especially fatigue after Q-fever are addressed in this thesis:

1. What is the occurrence at population level?
2. What are the consequences for daily activities and ability to work?
3. What is the current knowledge base with respect to the definition, diagnosis, aetiology, prognosis and best treatment for QFS?

Seeking answers to these questions, while working at the Municipal Health Service (MHS) Hart voor Brabant in the epicentre of this vast Q-fever outbreak, was the main inspiration to conduct these studies. Findings are considered relevant to patients, clinicians, medical microbiologists, the MHS and policy makers dealing with *C. burnetii*.

The outbreak

From December 2006 until spring 2007, five Q-fever cases were notified by the MHS Hart voor Brabant. As no cases had been notified by this MHS, in the previous 7 years, this was unusual. Clusters of patients with pneumonia, in May and June 2007, in two rural villages, Herpen and St. Oedenrode, were initially attributed to respectively *Mycoplasma pneumoniae* (*M. pneumoniae)* and *C. burnetii* [1]. As the clinical presentation of cases from both villages was similar, samples from Herpen were weeks later also tested for *C. burnetii* antibodies. Test results indicated that the outbreak in Herpen was not caused by *M. pneumoniae* but *C. burnetii*.

To facilitate control measures, the MHS focused on the identification of the cause of the outbreak and the affected geographical area/population. Questionnaires were used to identify a common alimentary or animal source. The rural outbreak region was dotted with animal husbandry enterprises in close proximity to human settlements. The Animal Health Service (GD) revealed that since 2005 [2] *C. burnetii* caused abortion storms in some dairy goat farms. The goat and sheep density in Noord Brabant was with 43 per km^2 the highest in the Netherlands (10 per km^2)[3]. Similar outbreaks implicating goats as the source had occurred in other countries such as Bulgaria [4] and Canada [5], but most Q-fever outbreaks for example in Germany [6] and the UK [7] were associated with sheep. Although not formally proven in 2007, goats seemed the likely source of this Dutch outbreak [8]. The 2007 outbreak was, at the time, considered a rare and one off event. However, the following years ever bigger seasonal annual outbreaks in a larger geographical area occurred with the MHS Hart voor Brabant at the epicentre.

Despite the implementation of veterinary control measures from 2008 onwards, including vaccination of dairy goats and dairy sheep, and hygiene measures, national notifications had increased to 4,026 cases by 2010 [9]. As the number of patients increased, so did the concerns of local professionals and the public. In November 2009, Q-uestion, a Q-fever patient organisation was founded [10]. Their agenda was to; inform Q-fever affected individuals on the infection, stimulate interaction between patients, promote research on long-term effects of *C. burnetii* infections and represent the interests of Q-fever patients in the political arena. The Q-fever outbreak received national attention in 2009 and culminated in a nationally broadcasted television program on the 6th of December 2009 [11]. Notwithstanding the veterinary measures taken, the large outbreak in 2009 indicated that these were insufficient. In order to prevent an even larger outbreak in 2010, in December 2009 the culling of more than 58,000 dairy goats [12] started on farms that tested Q-fever positive in a mandatory bulk tank milk monitoring programme.

Although the outbreak stopped, public concern did not. The Q-fever saga is ongoing, the Commission van Dijk presented an investigative report [13], the national ombudsman held a public hearing in 2012 [14] and Q-fever patients started a court case to seek compensation from goat farmers and the State [15].

Between 2008 and 2010 the MHS Hart voor Brabant notified 2,753 Q-fever cases, which was 40-53% of all their infectious diseases notifications which doubled their notification workload. During the same period 2,267 incoming Q-fever related telephone calls represented up to 36% of all received phone calls. These telephone calls from patients, occupational physicians, general practitioners (GPs), medical specialists, the press, and municipalities touched on aspects of chronic Q-fever and serological follow-up, the consequences of Q-fever on the general health status, in particularly fatigue and the effect on the ability to work.

Although the outbreak stopped five years ago, chronic Q-fever and the health status, especially fatigue post Q-fever remain important problems, with many unanswered yet relevant public health questions such as; is the follow-up after acute Q-fever adequate, is screening of the exposed general population indicated to identify chronic Q-fever? Can one develop a chronic infection after an asymptomatic Q-fever infection and how big a problem is Q-fever related impaired health status, especially fatigue?

Sequels of infection

Chronic Q-fever and the Q-fever fatigue syndrome (QFS) as sequels of infection.

1. CHRONIC Q-FEVER

Between 2 [16] and 5% of acute Q-fever patients develop chronic Q-fever [17, 18, 19]. As the then most recent article, the European Centre for Disease Prevention and Control (ECDC) risk assesment [16], stated 2% this percentage is used here in further calculations. Chronic Q-fever mainly presents as an endocarditis or a vascular infection with a high morbidity and mortality [20]. In the international literature, endocarditis is most often described but in this outbreak in the Netherlands, vascular infections are more common [21]. Among those most at risk to develop chronic Q-fever are individuals with cardiac valve pathology, aneurysms, vascular grafts and the immunocompromised [22]. The diagnosis is based on a combination of serology and clinical findings; a positive *C. burnetii* PCR analysis but not during acute infection, an IgG phase I antibody titre ≥1:1,024, presence of clinical risk factors and radiological imaging results including echocardiography and positron emission tomography-computed tomography (PET-CT) [23]. In order to detect chronic Q-fever (serological) follow-up is needed. Follow-up is especially important for the above mentioned patients with an increased risk to develop chronic Q-fever. The international literature, advised a follow-up strategy of three serological tests and echocardiography [24] for acute Q-fever patients. Part of the 2007-2008 cohorts of acute Q-fever patients were followed up accordingly but as no chronic infections were detected [25] the general echocardiographic screening was stopped. Raoult *et al*. [26] considered that decision premature because some heart valve defects are clinically silent (can only be detected with echocardiography) yet predispose patients for chronic Q-fever for at least 10 years post infection.

The approximately 300 voluntarily registered chronic Q-fever patients far exceeded the 80 (2% of 4,000 symptomatic notified Q-fever cases) expected cases. This would suggest that this sequel also occurred in the not notified *C. burnetii* infected individuals that had mild symptoms or were asymptomatic. The estimation was that every notified Dutch Q-fever case stood for 12.6 infections [27]. This would bring the total number of infections to approxi-

mately 50,000 (12.6 X 4,000) and the number of expected chronic Q-fever cases to 1,000 (2% of 50,000). If 2% chronicity is correct, this would suggest that many chronic Q-fever cases are not yet identified, or alternatively, that transition rates from acute to chronic infection are lower for the asymptomatic *C. burnetii* infected than for those with clinical acute Q-fever.

2. THE HEALTH STATUS, ESPECIALLY FATIGUE AND THE ABILITY TO WORK POST C. BURNETII INFECTION

In 1960 Powell [28] was the first to publishdata on long-term fatigue after Q-fever but it was Shannon [29] who introduced the term post Q-fever chronic fatigue syndrome in 1992. Syndrome, because the undue fatigue is accompanied [30] by many other nonspecific symptoms such as headache, disturbed sleep, night sweats, myalgia, arthralgia and blurred vision. The majority of international studies on QFS were small and follow-up was limited. In initial studies in the Netherlands, 52% of patients suffered from severe fatigue one year after the onset of Q-fever [31] and 37% after 2 years [32]. Important limitations of Dutch studies were the small sample size, control groups that were not serologically tested for Q-fever, were healthier than the general population, and the sole use of notified, symptomatic *C. burnetii* infected or MHS registered individuals.

The impaired health status and increased fatigue of Q-fever patients have a significant societal impact as work and private life are affected as a consequence [33, 34]. Patients, occupational physicians, GPs and the patient's organisation had many questions on how to interpret and deal with fatigue after Q-fever. This became such an important issue that the Ministry of Health requested the Dutch Centre for Infectious disease control (CIb) to write a national QFS guideline [35] that was finalised in 2012.

The outline of this thesis

Chapter 2 sketches the outbreak from 2007 to 2010, provides broad information on *C. burnetii* including diagnosis, veterinary measures and the general problems that patients with Q-fever might experience.

Part I. Studies on screening for chronic Q-fever. These are presented in chapters 3-5**. Chapter 3** depicts different follow-up strategies of three laboratories after an acute Q-fever infection, the knowledge of practitioners regarding serological follow-up of Q-fever, and the differences in follow-up rates. Due to the many Q-fever notifications in the Netherlands, the question arose what the best practice of follow-up screening for detection of chronic Q-fever could be. Therefore, a systematic review was conducted, see **chapter 4**. Was screening of the general population in a high prevalence area for chronic Q-fever indicated? Such a population screening was conducted in 2014 in the village Herpen and is described in **chapter 5**.

Part II. Studies on health status, especially fatigue and work. These are presented in chapter 6-9. **Chapter 6** provides information on the occurrence and impact of long-term complaints and absence from work whilst in **chapter 7** different aspects of the health status of notified Q-fever patients one to two years after notification are described. The health status of participants of a population survey in Herpen seven years after the start of the Q-fever outbreak is presented in **chapter 8.** Questions regarding the definition, aetiology, prognosis, prevention and treatment of fatigue or QFS after an infection with *C. burnetii* led to a systematic review **chapter 9**. The thesis is finalized with a summarising discussion in **chapter 10**.

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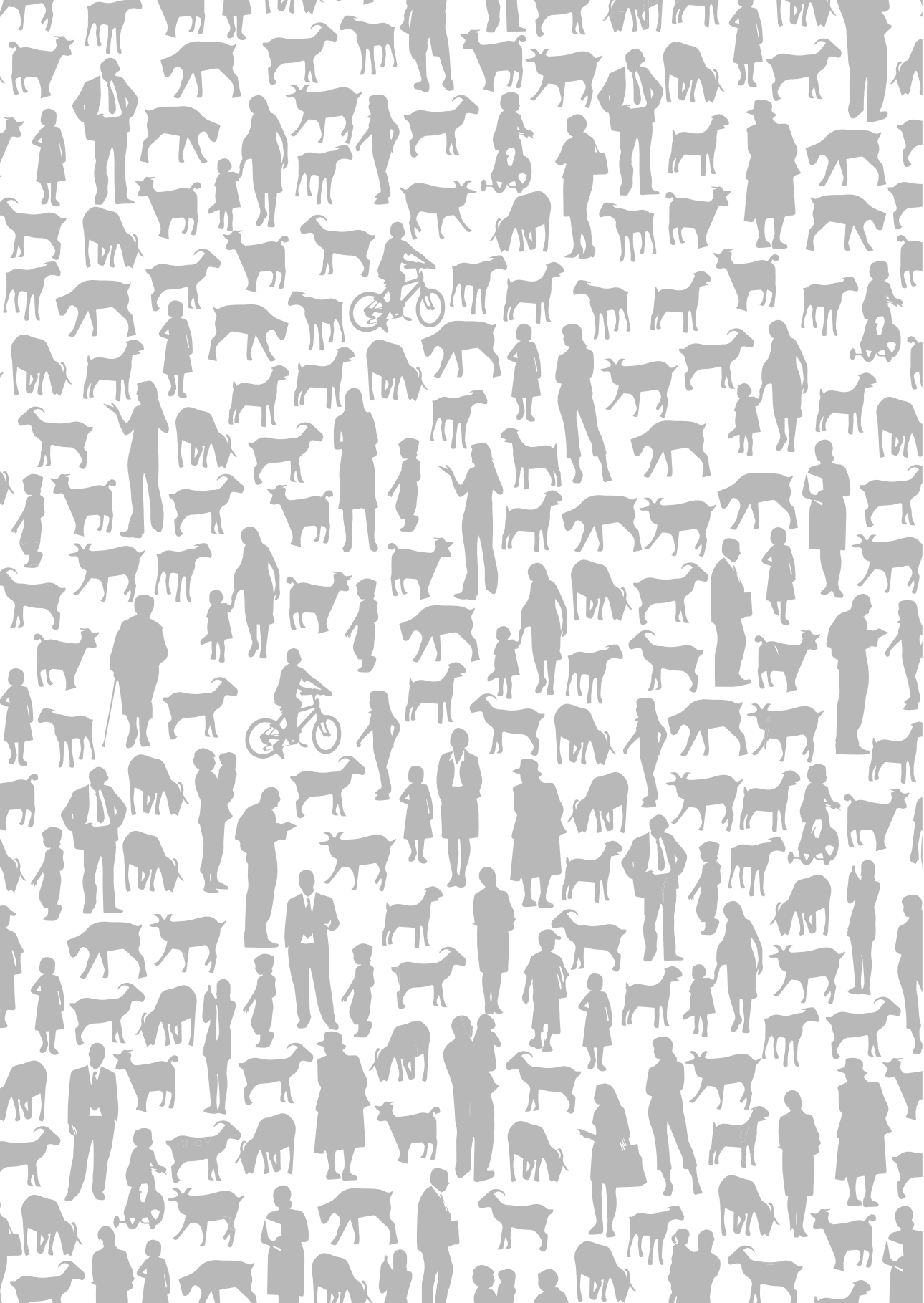

Chapter 2

2

EPIDEMIC Q-FEVER IN HUMANS IN THE NETHERLANDS

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ABSTRACT

In 2005, Q-fever was diagnosed on two dairy goat farms and 2 years later it emerged in the human population in the south of the Netherlands. From 2007 to 2010, more than 4,000 human cases were notified with an annual seasonal peak. The outbreaks in humans were mainly restricted to the south of the country in an area with intensive dairy goat farming. In the most affected areas, up to 15% of the population may have been infected. The epidemic resulted in a serious burden of disease, with a hospitalisation rate of 20% of notified cases and is expected to result in more cases of chronic Q-fever among risk groups in the coming years. The most important risk factor for human Q-fever is living close (<5 km) to an infected dairy goat farm. Occupational exposure plays a much smaller role. In 2009 several veterinary control measures were implemented including mandatory vaccination of dairy goats and dairy sheep, improved hygiene measures, and culling of pregnant animals on infected farms. The introduction of these drastic veterinary measures has probably ended the Q-fever outbreak, for which the Netherlands was ill-prepared.

INTRODUCTION

Since its first description in abattoir workers in Australia in 1935, Q-fever has been considered primarily an occupational disease for abattoir workers, sheep shearers, farmers, and veterinarians. Occasional outbreaks among the general population have been described in different countries but these were mostly confined to small areas and were of short duration. The 2007–2010 epidemic of Q-fever in the Netherlands with more than 4,000 notified human cases was unique. We describe the different aspects of this exceptionally large epidemic, primarily from the human health perspective, and provide details of ongoing research that will add considerably to the global knowledge base of Q-fever. Topics covered are the surveillance of acute Q-fever before and during the epidemic; the challenges in laboratory diagnostics; the long-term effects of Q-fever; prevention of severe disease by vaccination; risks for pregnant women; and the drastic veterinary measures on dairy goat and dairy sheep farms that were implemented from 2009 and that have probably played a major role in stopping the epidemic.

2. SURVEILLANCE OF ACUTE Q-FEVER AND DIAGNOSTIC CRITERIA

2.1 Q-fever as a rarity before 2007

The diagnosis of Q-fever was very rare in the Netherlands before 1977, despite increasing numbers of reported cases from other countries. Extensive studies were carried out between 1951 and 1956 on cattle (n = 524) and on patients with atypical pneumonia (n = 6,000). These studies tested serum samples using complement fixation test (CFT) and used animal (guinea pig) cultures. None of them revealed a positive result [1]. Then in 1956, just as these studies were being phased out, the first three human cases of Q-fever were diagnosed in the Netherlands [2, 3]. One patient worked at a slaughterhouse, one was thought to have been infected in Switzerland, and a third had spent time living near sheep. When 28 of these sheep were serologically analysed, one tested positive.

2.2 An increase in reported cases

In 1976 Q-fever was added to the list of notifiable diseases in the Netherlands. This was quickly followed by a rise in the number of reported cases – an average of 2–3 a year between 1977 and 1980, and an average of 20 a year up until 2007. Thirty-three Q-fever cases diagnosed between 1979 and 1983 have been described in more detail [4]. An in-house developed immunofluorescence assay (IFA) was used and IgM phase II ≥1:16 was considered reactive. Apart from the usual clinical presentation, epidemiological analysis to identify possible sources showed that 67% of these patients had acquired Q-fever in the Netherlands,

while the rest were probably infected in a variety of other European countries. However, a reanalysis of the data shows that the serologic profiles described in the patients diagnosed with acute Q-fever were quite heterogeneous, with mismatches of CFT and IFA results. Therefore, the group of patients described was a heterogeneous group with acute, past resolved and chronic infections.

2.3 Early seroprevalence studies

Within the context of increasing number of cases, extensive serologic studies were conducted in the Netherlands in the period between 1982 and 1985 [5-7], using CFT and IFA with *Coxiella burnetii* antigen phase II from Virion (Virion Ltd., Zurich, Switzerland). For IFA, IgG antibodies were tested to the phase II antigen, with a cut-off of ≥1:16. The study tested a selection of serum samples from groups of people considered to be at high risk of infection. This approach showed very high seropositive rates among veterinarians working with large domesticated animals (84%) and with small domesticated animals (77%), as well as taxidermists (70%) and wool spinners (58%). However, a range of high seropositivity rates (14–73%) was also found in the control groups. The authors suggest that these high rates were achieved because the IFA used in their study was more sensitive than the CFT used in previous studies. No control experiments with CFT were performed in this study, and the IFA results were not confirmed with additional titrations.

Unfortunately, the original data are not available for statistical reanalysis. If transmission rates in the 1970s and 1980s were high, then serologic evidence of this should be evident in older age groups in recent serological surveys. We speculate that the lack of specificity in the in-house IFA, combined with a low cut-off may have influenced the seroprevalence rates of this study.

2.4 The need for clearer analysis before the 2007 epidemic

When the Dutch Q-fever epidemic began in 2007, some speculated that the disease may have been previously overlooked because of under-diagnosis and misclassification, and that increased awareness had created a pseudo-epidemic through the misclassification of acute infections (Van Knapen, personal communication). Indeed, a considerable amount of misclassification is possible if diagnosis relies on detection of IgM phase II, which can persist for months or even years. Clearly, the pre-epidemic situation needed analysis. In addition a change in laws and regulations regarding infectious diseases in the Netherlands also started to have an impact.

2.5 Changing laws and regulations

The analysis of national data regarding disease incidence relies on notifications. Regulations that control notification are important as regulatory changes can influence epidemiological

curves. When Q-fever was added to the list of notifiable diseases in 1976, clinicians were legally required to notify public health authorities of Q-fever patients, and municipalities (advised by municipal health services) were obliged to enforce legal actions to curb epidemics when necessary. The use of the Q-fever notification system was analysed in 2002 [8]. Aggregated data from between 1988 and 2002, retrieved from laboratories, hospital admissions and discharge records, were compared to the national data set of Q-fever notifications. This analysis showed that only 50% of diagnosed cases were reported by clinicians because laboratories were not required to provide notification at that time. In 2008, a new law was introduced in the Netherlands to comply with international health regulations. According to this law, laboratories were also obliged to provide notification. This approach was expected to improve notification records – as each case would be notified by both the laboratory and the consulting clinician.

2.6 Possible Q-fever clusters before 2007 detected retrospectively

Clinical Q-fever in animals was diagnosed in the Netherlands in 2005 in two dairy goat herds with high abortion rates [9]. Van den Wijngaard *et al*. [10] speculated that unrecognised outbreaks might have preceded the first recognised outbreak in 2007. With this in mind, they used space-time scan statistics and syndromic surveillance to search for hidden Q-fever clusters before and during 2007. Hospitalisation data for lower respiratory, hepatitis and endocarditis infections occurring between 2005 and 2008 were aggregated by week, age group and postal codes. Alternative causes of outbreaks were excluded by reviewing all mandatory notified diseases with similar clinical presentation in the same period. Surveillance data on influenza-like illness were also included to assess whether clusters of hospital admissions for lower respiratory tract infections could be due to influenza. From 2005 to 2008, a total of 20 lower respiratory tract infection clusters and two hepatitis clusters were detected. Scan statistics for space-time clusters detected one specific cluster- the Q-fever epidemic in 2007. However, ten other clusters were also detected that could be due to other causes, including a major confirmed Legionella outbreak. Three clusters which occurred earlier than the recorded outbreak – two in 2005 and one 2006- could be due to Q-fever because there was a Q-fever-affected farm nearby and there was no alternative explanation for the cluster. In 2007, a number of clusters of lower respiratory tract infection and one hepatitis cluster were also found, and could be attributed to the actual Q-fever epidemic. Three clusters in 2007 could not be attributed to Q-fever, because they could not be linked to Q-fever abortion waves on farms.

In conclusion, Q-fever may have spread unnoticed among humans before 2007, and routine cluster scanning may facilitate earlier detection of comparable epidemics in the future. There is indeed circumstantial evidence of limited clustered spreading of *C. burnetii* among humans before 2007, but this analysis also confirms that the major outbreak started in 2007.

However, once the Q-fever epidemic was established, it may have resulted in an increased number of diagnoses, influencing epidemic curves **[**11].

2.7 Recent serosurveillance: The PIENTER Study

In 2006, a population-based seroprevalence study was carried out by the National Institute for Public Health and the Environment to evaluate the Dutch National Immunisation Programme. This programme (PIENTER) has been described in detail by van der Klis *et al*. [12]. It was a national survey in which participants were asked to donate blood and complete a questionnaire on demographics, health perception and activities related to infectious diseases. Data and sample collection was finalised in June 2007, after which the stored serum samples were used to screen for the presence of *C. burnetii* antibodies [13].

Given the screening considerations described above, this study used a combined test strategy to measure seroprevalence, using an enzyme-linked immunosorbent assay (ELISA) IgG phase II (Serion Immundiagnostica, Würzburg, Germany) on the study group of 5,654 samples, followed by a confirmation of positives by IFA (Focus Diagnostics, Cypress, California, USA). IFA was also used to estimate the ELISA's false negative rates on 504 randomly chosen ELISA negative samples.

Of the 5,654 samples tested, 85 were positive with the ELISA IgG phase II. Of these, 47 had borderline levels and 15 were negative in an IFA IgG phase II screened with 1:32. This resulted in a seroprevalence of 1.5% using ELISA to screen and IFA to confirm. In the 504 ELISA negative samples tested in IFA, six (1.2%) had titres ranging from 1:32 to 1:128. Using IFA as the 'agreed standard', the adjusted seroprevalence estimate was 2.4%. These results underscore the problems encountered while comparing different seroprevalence studies.

The results from this study yielded a low seroprevalence in the Netherlands before 2007, but the low numbers still represent a considerable amount of exposure. Seropositivity in males was higher than in females and increased with age. No regional differences were observed, even when sheep, goat and cattle densities were examined. However, higher seroprevalence was associated with increasing age, being born abroad (specifically in Turkey), keeping ruminants and having occupational contact with animals. In conclusion, this study supports the concept of the massive localised introduction of *C. burnetii* in the human population from 2007 onwards [13].

Clearly, Q-fever has been circulating at a low level in the Netherlands since the 1950s. There may have been a temporary increase in exposure during the 1980s, but data from older sero-surveys and notifications may lack accuracy. Recent studies confirmed a massive exposure of Q-fever in the Netherlands from 2007 onwards.

3. THE DUTCH EPIDEMIC FROM 2007 TO 2010

3.1 Concerns rise in 2007

Between March and June 2007, six cases of acute Q-fever were notified by regional microbiology laboratories to public health authorities in the province of North Brabant in the south of the Netherlands. These patients were admitted with atypical pneumonia to a number of hospitals in the province. Concerned, the regional Municipal Health Service (MHS) analysed the cases in detail, but could not link them epidemiologically. Then a general practitioner from a nearby village reported an excess of patients with pneumonia at his practice. Initially, these patients were mistakenly thought to have *Mycoplasma pneumoniae* infection due to serologic cross-reactions, but they were eventually confirmed as having acute Q-fever in July 2007 [14; 15].

Eventually, a total of 168 human cases were notified in North Brabant in 2007. Dairy goats were identified as the source of the human Q-fever cases in North Brabant- the Animal Health Service confirmed a considerable number of Q-fever- induced abortions at several farms in the region. The unusually hot and dry weather in the spring of 2007 may have caused airborne transmission of contaminated dust particles. The outbreak seemed to have been concentrated around a single village, but a specific point source could not be identified. A case-control study was performed in the village [16] and contact with manure, hay and straw were shown to be risk factors. It was shown that people living in the eastern part of the village close to ruminant farms (one of which had a recent history of abortion problems) were at a higher risk than people living in other parts of the village. Contact with animals and the consumption of raw milk products were not significant risk factors in the multivariable analysis. In general, acute Q-fever seemed not to be related to the working environment but there were reports of incidental cases that occurred after visits to dairy goat farms with abortion problems.

3.2 Source of epidemiological data

The source of epidemiological data is the national registry of notifiable infectious diseases. Attending physicians and heads of microbiology laboratories have a legal obligation to notify the diagnosis of human Q-fever to the MHS, which enters the cases into an anonymous national electronic database ('Osiris') monitored by the Centre for Infectious Disease Control. Since the beginning of 2007, notification criteria for acute Q-fever in Osiris have been a combination of clinical presentation matching Q-fever, with either a four-fold IgG titre rise or a positive IgM phase II antibody test measured by IFA, ELISA, or CFT. During the course of the outbreaks, certain adaptations were made to the notification criteria. In July 2008, a clinical presentation matching Q-fever was further defined as fever, or pneumonia, or hepatitis. In February 2010, an additional laboratory criterion was the detection by polymerase chain reaction (PCR) of *C. burnetii* DNA in

serum or respiratory material. However, diagnoses based on PCR were already accepted before that time. Given the above criteria, misclassification was possible when isolated IgM was used as a sole measure, since IgM can be a false positive, or persist for months after a past resolved infection. Moreover, clinical symptoms may be nonspecific.

Another important source of epidemiological data was a questionnaire routinely dispatched to notified acute Q-fever cases by the MHS, which included questions about environmental risk factors and clinical characteristics. This questionnaire was received from 74% of notified cases with onset of illness in 2007 and from 93% of notified cases with onset of illness in 2008.

3.3 2007–2010 Overview: not an isolated incident

As the number of notifications increased from May 2008, it became evident that the 2007 outbreak was not an isolated incident. A total of 3,489 Q-fever patients who experienced onset of disease between 2007 and 2009 were notified. Of these, 194 cases had a date of onset in 2007, 982 in 2008, and 2,313 in 2009. The epidemic curve (Fig.1) shows a seasonal pattern, with most cases occurring in spring and early summer. The highest incidences were seen in the south of the country, mainly in the province of North Brabant; the affected area expanded to the north and the south during the epidemic (Fig.2). Patient characteristics from 2007 to 2009 were presented by Schneeberger *et al*. [17]. The median age of the confirmed notified patients was 50 years, and > 60% were male.

The additional MHS questionnaires showed that only a small proportion of patients lived on a farm or worked in the agriculture or meat processing sectors. However, notified patients frequently reported that they had been in contact with a diverse number of animals and animal products.

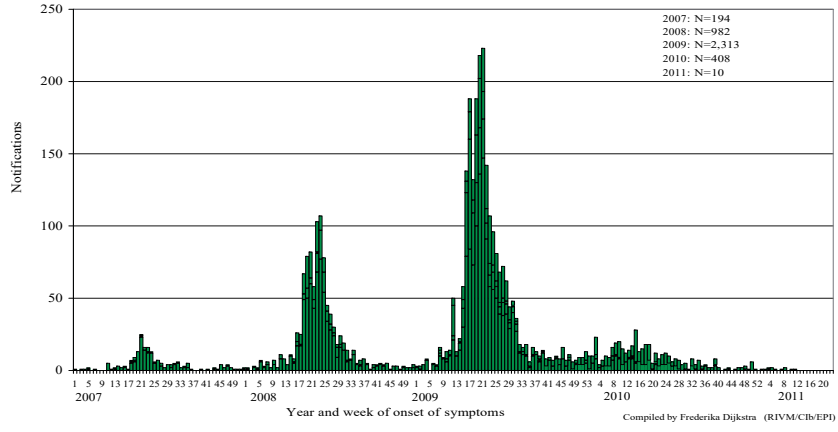

Fig. 1 Number of notified acute Q fever patients from 1 January 2007 to 23 March 2011 with known day of onset of illness

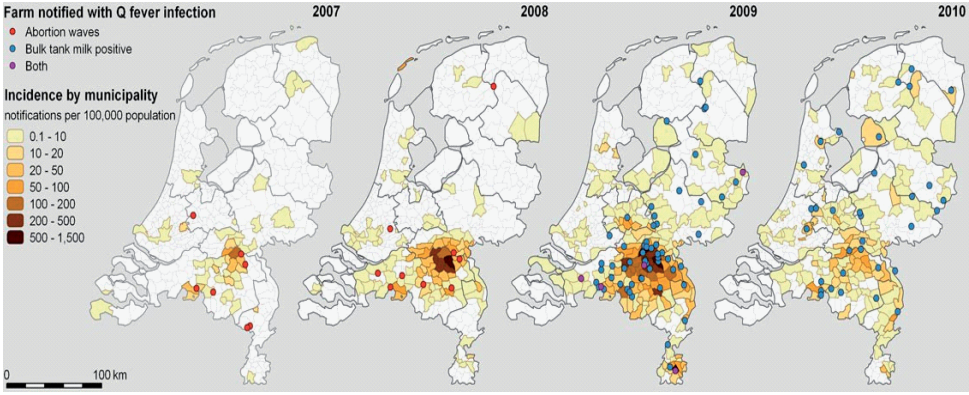

Fig. 2 Annual incidence of acute Q fever by municipality and location of infected farms. Incidence is based on year of onset of illness of notified acute Q fever patients

In 2007, the percentage of hospitalized patients (50%) was largely influenced by active case findings in a retrospective survey among hospitalised cases [18]. In 2008 and 2009 it was 20%, still much higher than the 2-5% hospitalisation rate reported in the literature [19]. Fever was the most frequently reported symptom (92%), followed by fatigue (78%) and headache (69%). Pneumonia was diagnosed in 62% of patients, while endocarditis (3%) and hepatitis (<1%) were relatively rare. Underlying diseases were frequently reported. Almost 49% of patients smoked, which is relatively high compared to percentages in the general population (30% for males and 24% for females, according to Statistics Netherlands).

3.4 Diagnostic delay and influence of influenza A (H1N1)

All notified patients in 2007 for whom additional laboratory data was available were diagnosed either by IFA or CFT. In 2008, 3% of cases were diagnosed by PCR. The most popular method in 2008 was still IFA (75%), although CFT, ELISA, PCR and other methods were also used. In 2009, 79% of notified patients were diagnosed serologically and 20% by PCR. IFA was used in more than half of the cases in 2009, CFT was used in more than a quarter of the cases and ELISA was used in 14% of cases.

The median diagnostic delay (the delay between the date of onset of illness and the date of *C. burnetii* diagnosis) decreased from 82 days in 2007, to 28 days in 2008, to 20 days in 2009 [11]. The diagnostic delay was due to lack of awareness by medical staff and the delay in making a definitive diagnosis, as routine diagnostics mainly relied on seroconversion in convalescent serum. Increased awareness and improved routine laboratory services, such as the introduction of IFA, ELISA, and in 2009 PCR, have reduced this diagnostic delay.

Under conditions of high incidence, the positive predictive values of tests are very high. In the autumn of 2009, pandemic influenza A (H1N1) 2009 with more or less similar symptoms interfered with the analysis of the Q-fever epidemic. In this third year of the Q-fever outbreak, a high background prevalence of antibodies to *C. burnetii*, specifically positive IgM titres, were common in most of the affected areas. This made it much more difficult to determine the exact start of an acute Q-fever episode, thus making notifications less reliable. In fact, many patients diagnosed in the laboratory in 2010 had probably experienced clinical signs of acute Q-fever much earlier. Under these circumstances, the persistence of IgM makes it difficult to measure the actual decline of the incidence of the disease.

3.5 A link with goats and sheep

In May 2008, an outbreak of Q-fever occurred in a psychiatric care institution in Nijmegen near the 2007 outbreak area [20]. At least 28 in-patients, staff, and visitors had laboratory confirmed Q-fever illness and several patients in the institution developed atypical pneumonia. It was discovered that these patients had been in close contact with lambs as part of their therapy sessions. Then a large number of goats unexpectedly aborted their offspring on a farm close by, and Q-fever was confirmed in the farmer and his wife living there [14]. An urban cluster identified in 2008 was found to be related to a goat farm with high abortion rates in the area. Patients lived downwind of the goat farm and a house located <2 km from the farm was associated with a higher risk of Q-fever infection, compared to a house located at ≥ 5 km [21]. In 2009, 59% of notified human cases lived within a 5 km zone of a bulk tank milk-positive dairy goat or sheep farm, and 12% (roughly one million people) of the Dutch population lived within such zones [14;18]. The available evidence in the Netherlands points to dairy goat farms with Q-fever-induced abortion problems as the main source of the human outbreaks with a smaller role for dairy sheep and non-dairy sheep.

3.6 Transmission from animals to humans

Infection of humans is caused by inhalation of contaminated aerosols that can spread over some distance. Especially when infected pregnant small ruminants abort, billions of *C. burnetii* end up in the environment while fewer than 10 organisms are sufficient to seed an infection [22]. The organism's ability to persist in the environment may result in a continued risk for infection weeks to months after the birthing event.

The size of the community outbreak in the Netherlands suggests that transmission predominantly takes place through wide-scale environmental contamination or multiple point-source contamination sites. There is strong epidemiological evidence that most human cases are caused by abortion waves on dairy goat farms. People living close to such farms are at risk. Infected farms that have no abortion waves can still be infectious when there is close contact with animals. The transmission route is the same, through inhalation of contaminated

aerosols, but the dose is much lower, hence closer contact is required for infection. Based on detailed information from notified patients, occupational exposure can explain only a small proportion of the acute Q-fever cases in the Netherlands.

Despite the evidence pointing towards dairy goat farms with Q-fever-induced abortion problems, there were a number of such farms without any human cases in the surrounding population. In the 5 km areas around 27 farms with clinical abortion problems, environmental data sets were collected. This showed clear differences between areas with and without transmission to humans in vegetation density and in average groundwater conditions [23]. Areas without transmission had higher vegetation densities, based on remotely sensed satellite imagery, and relatively shallow groundwater conditions suggesting that vegetation and soil moisture are relevant factors in the transmission of *C. burnetii* from infected small ruminant farms to humans.

Alternative routes of transmission are unlikely to have played an important role. Q-fever is a zoonotic disease with no convincing evidence for human-to-human transmission. Information from notified acute Q-fever patients makes it very unlikely that consumption of unpasteurised dairy products has played an important role. In 2008 the manure streams from dairy goat farms were investigated in some detail. Manure was often transported to other parts of the country to be used for example in flower bulb cultivation but in the recipient areas no Q-fever cases were reported (unpublished data). It was therefore concluded that manure did not play an important role. More than 2000 ticks have been collected from sheep and the environment but no *C. burnetii* was detected. Dairy goats in the Netherlands are kept indoors in deep litter stables and are not affected by ticks.

4. VETERINARY CONTROL MEASURES

4.1 The Veterinary situation at the beginning of the outbreak

The world's largest Q-fever epidemic recorded to date occurred in an area densely populated with people and domesticated animals, suggesting that animal farming in such areas poses a risk for zoonotic diseases such as Q-fever in humans. Initially, the evidence to link the outbreak to goat farming was largely circumstantial, in the absence of DNA fingerprinting techniques for *C. burnetii* that could have matched bacteria from human and animal samples. While there was no sound evidence base for control measures, the subsequent rapid expansion in the scale of the epidemic was unforeseen. National and regional public health authorities were largely unprepared for an outbreak of this magnitude, and international literature on smaller outbreaks provided insufficient guidance on several key issues - such as appropriate control measures, the possible effects of the epidemic on pregnant women, the most adequate therapy for acute Q-fever, the identification and classification of chronic Q-fever,

and the use of the Australian human vaccine for Q-fever. The most affected province, North Brabant, has a surface area of 5,100 km^2 and currently houses 2.4 million people and 6.4 million livestock (80,000 sheep, 135,000 goats, 660,000 cows and 5.5 million pigs) [24], with a goat density that increased five-fold between 1990 and 2007. In retrospect, abortion waves due to *C. burnetii* infection among the goat population were reported from 2005 onwards, although they were not recognized as such at that time.

4.2 Veterinary measures in response to the 2008 outbreak

The widespread pattern of the outbreak in 2008 was alarming and pointed to several clusters with multiple sources. In June 2008, the government announced the mandatory notification of Q-fever on dairy goat and sheep farms with >5% abortions due to *C. burnetii* infection, and introduced appropriate hygiene measures [25]. During a period of 90 days following the detection of Q-fever at a farm, a manure removal ban and visiting restrictions were implemented [25].However, no restrictions on the trans- port of animals from infected farms were imposed, and other possible veterinary measures to contain the outbreak, such as a breeding ban, were not included.

Then, in October 2008, the Dutch government authorised the voluntary vaccination of animals on large dairy goat and sheep and recreational farms using the non-registered Coxevac® vaccine (Ceva Santé Animale, France). From November 2008, goat and sheep at smaller farms were also vaccinated. However because of limited vaccine availability – just 80,000 doses – vaccinations could only be provided within a 45 km radius of the outbreak source. In February 2009, a nationwide hygiene protocol became mandatory for all dairy goat and sheep farms, whether infected or not [25]. The eradication of vermin became compulsory, the cleaning of stables during lambing season and for 30 days afterwards was forbidden, and manure had to be stored and covered for at least 90 days before use.

4.3 Veterinary measures in response to the 2009 outbreak

Despite these measures, the outbreak was still far from contained. Over 2,000 new human acute Q-fever cases were notified from late March 2009 onwards, in a larger area than in 2008. In response, in April 2009, the government extended the vaccination campaign to include a compulsory vaccination programme [25]. Farms with a public function and dairy goat and sheep farms with more than 50 animals in the epidemic centre had to vaccinate their animals before 2010. All Q-fever infected farms outside of the area were also obliged to vaccinate their animals. Vaccination of animals on farms in the rest of the Netherlands was still on a voluntary basis. In July 2009, the pasteurization of manure for a minimum of 1 hour at 70°C was permitted instead of a decomposition period of 90 days [25]. Restrictions

on incoming and outgoing animal transport on *C. burnetii* infected farms were imposed from October 2009 onwards [25].

4.4 Bulk tank milk monitoring

Also from October 2009 onwards, the government set out a new strategy to identify infected farms that did not have an abortion rate above 5%. Farms with more than 50 dairy goats or sheep were obliged to participate in Q-fever bulk tank milk monitoring [25]. Bulk milk tanks were sampled once every 2 months (and later on once every 2 weeks) and tested for the presence of *C. burnetii* DNA using a real- time PCR by the Animal Health Service. To separate infected farms from non- infected farms, a cycle threshold (Ct) of 36 as detected by a-real-time PCR test targeting IS1111 was used. This threshold, which was set arbitrarily, is close to the detection limit of real-time PCR tests, implying that the outcome of the test in the lower range (from Ct 34 to 36) is determined stochastically. Positive samples were forwarded for confirmatory testing to the Central Veterinary Institute, and confirmed farms were declared infected. Infected farms were identified on the basis of a positive PCR outcome only, as information on background values of *C. burnetii* DNA load in goat bulk tank milk samples was unavailable. This approach may well have resulted in farms being declared infected when they posed no threat to human health.

4.5 Drastic veterinary measures

In December 2009, Zembla, a current affairs television programme co-produced by the Dutch Broadcasting Association and a Dutch public newscaster, raised critical concerns about the role of the Dutch government in containing the Q-fever outbreak. The Dutch government responded to the increasing concerns by administrators, professionals, and the public by making the location of the 55 *C. burnetii*-infected farms public, announcing a breeding ban on infected farms, and increasing the frequency of tank milk monitoring from bi-monthly to bi-weekly [25]. The decision was taken to implement the most radical measure possible, the pre-emptive culling of all pregnant goats on infected farms [25]. Male goats on infected farms were also culled, as they could supposedly transmit the disease via semen.

A total of 50,355 goats and sheep were culled from 21 December 2009 to June 2010 on 89 bulk tank milk positive farms. Of 517 culling-workers, involved, 17.5% seroconverted for antibodies to *C. burnetii* despite use of personal protective equipment [26]. Seroprevalence of *C. burnetii* in workers before the culling activity was 13%, which is similar to findings among blood donors residing in the high-incidence area in the Netherlands in 2009 and in similar high-risk occupational groups internationally [27]. Symptomatic infection was recorded in 31% of the seroconverters. A strong dose-response relationship was shown between risk of seroconversion and number of hours worked on the farms and working inside the stable (in close proximity to the animals). In other settings internationally, a risk-gradient has also

been shown with close direct and indirect animal contact over time [28; 29]. Given the high risk of infection during culling activities, additional preventive measures should be taken. The Health Council of the Netherlands (2010) [30] has already issued a first advice on risk groups suitable for human vaccination against Q-fever. However this advice does not extend to culling workers.

4.6 Effect of veterinary measures in 2010

Exponential spread of Q-fever did not occur during the spring of 2010, as feared. Still, almost 400 new Q-fever patients were diagnosed during that year. By June 2010, all dairy goats and sheep had been vaccinated twice with Coxevac, and on July 15th the breeding ban for non-infected farms was lifted. The reason for the approximately five-fold decrease in the number of human infections between 2009 and 2010 is mainly attributed to the culling of pregnant goats and sheep, and the vaccination programme. Other factors could have contributed such as hygiene measures, climate, and increasing immunity among the general population.

4.7 Identification of the source of the outbreak

Recent genotyping studies point to a multi-strain bacterium in both livestock and humans [31] as the cause of the Dutch Q-fever outbreak and not simply one highly virulent *C. burnetii* strain. Several conditions may have favoured the introduction and rapid spread of *C. burnetii* among livestock in the Netherlands since 2005. In general, goats are kept in large herds in 'deep litter stables' - stables on concrete floors with pits. Straw is regularly added to these deep litter stables, which allows for relatively unhygienic conditions as potentially infected excreta such as urine, faeces and birth products are not regularly removed. Furthermore, the straw is often bought from countries such as France and Germany, which might be a source of *C. burnetii*. Relatively high quantities of *C. burnetii* DNA were measured in samples of stocked straw that had not yet been used in deep litter stables (unpublished observation of MHA Hermans and PC Wever).

New-born goats are often fed raw cow colostrum. Colostrum is the highly nutritious milk produced by mammals just before giving birth, and cow colostrum may contain large quantities of *C. burnetii* DNA (unpublished observations of MHA Hermans and PC Wever). Therefore, the role of straw and colostrum are interesting for further investigation as potential sources of multi-strain *C. burnetii* infection in goats.

When the pits in deep litter stables are full – which happens two or three times a year – everything (including manure and birth products) is removed and spread over the fields or transported elsewhere. Furthermore, the open air stables allow wind to blow through and carry *C. burnetii*-infected dust into the environment. April 2007, May and June of 2008, and April 2009 were unusually dry by Dutch standards – this type of weather condition combined with wind has been documented to play an important role in other Q-fever outbreaks [32].

5. LABORATORY ISSUES

5.1 The optimization of acute Q-fever diagnostics in the Netherlands during an outbreak

Prior to recognition of the Q-fever outbreak in 2007, Q-fever diagnostics were performed by a limited number of Dutch microbiology laboratories. The National Institute for Public Health and the Environment functioned as a reference laboratory using the IFA as a reference method, while other regional microbiology laboratories used the CFT. Following recognition of the scale of the outbreak, mid 2007, a number of microbiology laboratories in the epidemic area began to offer Q-fever diagnostics. The laboratories chose to use either IFA or CFT, depending in part on the type of serologic assays already in use by them. Seroconversion can be detected earlier by IFA compared to CFT (between 10 and 15 days after infection, versus 2–3 weeks, respectively). In addition, IFA allows the separate analysis of IgM and IgG antibodies against *C. burnetii* phase II and phase I antigens (IgM-II, IgG-II, IgM-I and IgG-I antibodies). Analysis of these four antibodies makes it possible to identify various stages in the acute Q-fever infection. The presence of solitary IgM-II antibodies – the first antibody to appear in the serologic response – indicates early acute infection, whereas the presence of IgG-II, IgM-I and IgG-I antibodies reflects a later stage of acute infection. CFT, in contrast, has been reported to be less prone to false positive results than IFA, especially with detection of IgM-II antibodies. Both methods are labour-intensive, non-automated and subject to inter- and intra-observer variation [33; 34].

An important drawback to the serological diagnosis of acute Q-fever is the lag phase in antibody response of up to 3 weeks after the onset of clinical symptoms. In 2008, the ongoing outbreak resulted in the development of real-time PCR assays targeting the multi copy IS1111 insertion element by several microbiology laboratories. These assays were used for the detection of *C. burnetii* DNA in serum, respiratory samples, urine specimens, tissues and amniotic fluids. Subsequently, an inter laboratory evaluation of different DNA extraction and real time PCR methods for the detection of *C. burnetii* DNA in serum was conducted. Overall, a low degree of variation was observed in the sensitivity of the evaluated real time PCR assays, although assays amplifying short DNA fragments yielded better results than those producing a large DNA fragment [35]. Next, performance of one of the PCR was evaluated retrospectively on serum samples of acute Q-fever patients at various stages of the serological response. *C. burnetii* DNA was detected in serum from 98% of seronegative acute Q-fever patients and in 90% of patients with solitary IgM-II antibodies. Ultimately, the PCR became negative as the serological response to *C. burnetii* further developed, with subsequent appearance of IgG-II, IgM-I and IgG-I antibodies [36].

5.2 Increasing diagnostic demands

To cope with the surge in diagnostic demands, which occurred during 2009 (e.g. over 18,000 requests for Q-fever diagnostics were received by one single laboratory), several microbiology laboratories in the epidemic area began using algorithms to provide accurate, fast, cost-effective and standardized acute Q-fever diagnostics. One such algorithm used an ELISA for IgM-II antibodies, performed on an automated processing system as an initial screening step. In the case of a positive or dubious ELISA result, IFA was performed as a confirmation step. PCR was performed after a negative ELISA result and when the serum sample was either acquired ≤14 days after onset of disease or referred by a hospital physician (noted for their lack in providing a date of onset of disease). When acute Q-fever diagnostics on the first serum sample were non-conclusive, a second serum sample was requested after 14 days. Overall, this diagnostic approach led to a significant reduction in the number of labour-intensive, non-automated IFA tests performed, with an increased diagnostic yield on first serum samples due to the introduction of PCR techniques. Likewise, an algorithm was introduced using the ELISA for IgM-II antibodies as a screening step followed by CFT as a confirmation step [37].

5.3 A consensus on Q-fever diagnosis

In 2010, the National Institute for Public Health and the Environment and the Dutch Society for Medical Microbiology formed a working group to develop a consensus on the microbiological diagnosis of acute Q-fever. In September 2010, a consensus document was published recommending the use of algorithms in which PCR, ELISA for IgM-II antibodies and either IFA or CFT were incorporated [34]. The diagnosis 'confirmed acute Q-fever' is established by a single positive PCR result with an appropriate clinical presentation or an IgG-II seroconversion or a four-fold or higher increase in IgG-II titre detected by IFA or CFT (requiring multiple serum samples). The diagnosis of 'possible acute Q-fever' is made by a positive IgM-II result (in the presence or absence of IgG-II, IgM-I, IgG-I antibodies) in a single serum sample with an appropriate clinical presentation and should be confirmed by either an IgG-II seroconversion or a four-fold or higher increase in IgG-II titre in a follow-up serum sample. The introduction of the term 'possible acute Q-fever' was the result of an increasing number of patients with past resolved Q-fever and persisting antibody titres against phase II antigens in particular, as well as reported false-positive IgM-II results from IFA and ELISA.

5.4 Cross-reactions in serologic tests for Coxiella burnetii

While screening methods should be very sensitive and can be less specific, several screening methods for infectious diseases have shown cross-reactions with other infections. For Q-fever, most cross-reactions described in the literature are those with other agents, which cause pulmonary infections such as *Legionella pneumophila* [38; 39].

In the Netherlands, patients with a pulmonary infection are usually screened for several pathogens. This approach recognises cross-reactions with other agents that cause pulmonary infections. The Q-fever epidemic in the Netherlands was first thought to be caused by *Mycoplasma pneumoniae*, because CFT results of several patients showed low titres against this organism. Therefore, we investigated cross- reactions between sera from patients with high Mycoplasma titres and the ELISA screening assay for Q-fever. No cross-reactions were found.

Cross-reactions with other pathogens are less likely to be recognised. We investigated cross-reactivity in sera taken from patients with recent *Epstein-Barr* virus (EBV) and *Cytomegalo* virus (CMV) infections (IgM positive with low avidity). In a *Coxiella* screening ELISA (IgM phase II), 16/72 EBV IgM positive sera reacted while 7/33 CMV IgM positive sera reacted. In both EBV IgM- and CMV IgM-positive patients, the results in the Q-fever ELISA were generally low positive. When performing an IFA phase I and II assay on the ELISA positive samples, all EBV IgM positive patients became negative. However, 40% of CMV IgM positive patients also had positive IFA tests and we concluded that these patients probably had two infections going on at around the same time.

When screening patients with a proven seroconversion for *C. burnetii*, we found very few cross-reactions in tests for EBV IgM (2%) but somewhat more in tests for CMV IgM (8%). Unfortunately, we were unable to follow these patients up to see if these were true double infections or not. We concluded that recent EBV and CMV infections can cause cross-reactive antibodies against *C. burnetii* in ELISA tests, but not in IFA tests. It is possible that a recent Q-fever infection can also cause cross- reactions in the test for CMV IgM. Therefore, screening with ELISA, followed by confirmation with IFA, is a good way to exclude false positive tests for *C. burnetii* due to recent EBV and CMV infections.

5.5 Seroprevalence surveys

Strategies for diagnosing acute and chronic Q-fever in individual patients differ from population-based seroprevalence surveys. Acute Q-fever is diagnosed mainly by the detection of antibodies of IgM and IgG subclasses against phase II of *C. burnetii*. The diagnosis of chronic Q-fever relies on high titres of phase I IgG antibodies; the sole presence of phase II IgG antibodies against *C. burnetii* indicates a previous infection [40; 41]. IgG-II antibody levels remain constantly high for almost a year and then slowly decrease, remaining detectable for years after first detection [42]. Therefore, the study of seroprevalence relies on the detection of IgG-antibodies against phase II of *C. burnetii* in serum samples– antibodies can be detected by CFT, IFA or ELISA. What we need to establish is: which test works best?

5.6 The IFA/ELISA debate: the need for a standard

Studies in the late 1980s and early 1990s reported that the ELISA was a more sensitive and specific method than either the IFA or CFT [43 - 45] evaluated the performance of an ELISA

IgG kit (Panbio) against an in-house IFA. The two tests had moderate (53%) agreement; the ELISA had a sensitivity of 71% and a specificity of 96%. A number of different in-house IFAs were evaluated against ELISA, using different methods and cut-offs [46- 47] and the results are illustrative of the difficulties in comparing studies of the serodiagnosis and seroprevalence of Q-fever. Nevertheless, IFA has been proclaimed the gold standard reference method in the literature [48], although this method is laborious when compared to the ELISA (which is easier to automate and more suitable for testing large sample numbers). Commercial ELISA and IFA tests are both in current use for the diagnosis of acute and chronic Q-fever and in seroprevalence studies globally [49- 51]. The uncertainty regarding a valid standardised test, coupled with insufficient knowledge about the specific fate of antibodies against *C. burnetii* makes the sero-epidemiology of Q-fever a difficult undertaking.

Serum samples from a case-control study conducted in 2007 in the Netherlands to investigate the source and routes of transmission in this outbreak were used to evaluate the performance of one commercially available ELISA (Serion Immundiagnostica, Würzburg, Germany) and one IFA (Focus Diagnostics, Cypress, California, USA). Four hundred and eighty-seven human sera were evaluated in terms of sensitivity, specificity and kappa value. The sensitivity and specificity of ELISA for the detection of IgG phase II antibodies were 59% and 97%, respectively [52]. Seroprevalence varied depending on the method used; it was 12.7% when tested with IFA and 6.2% when tested with the ELISA. When measuring IgM antibodies to phase II Coxiella antigen, the two tests were comparable, with a kappa value of 0.89. Sensitivity was 82% and specificity 100%. These results sup-port the concept that the ELISA performs reasonably well when diagnosing acute Q-fever. However, in past infections, as defined by the sole presence of IgG antibodies, low positive samples have been missed by ELISA. More longitudinal studies using different test systems are needed to measure the levels of antibodies to *C. burnetii* in human serum. A single standard must be agreed on and defined in order to be able to easily compare results from various sero-surveys.

6. Q-FEVER AND PREGNANCY DURING THE 2007–2010 Q-FEVER OUTBREAKS IN THE NETHERLANDS

6.1 The international literature

When it became apparent that Q-fever had become a major problem in the Netherlands from 2007 onwards, discussion arose about the health threat to pregnant women [18; 53]. An estimated 90% of acute Q-fever infections in pregnancy present without clinical signs, which is much higher than among non-pregnant persons. International literature suggests that untreated acute Q-fever infection during pregnancy may result in adverse pregnancy outcomes in up to 81% of cases [54- 56]. These outcomes include abortion or intra-uterine

foetal death and pre- mature delivery or low birth weight. Furthermore, the risk of developing chronic Q-fever infection is reported to be higher in pregnant women [33; 57]. The only way to detect subclinical Q-fever is through screening of serum for antibodies to *C. burnetii*.

6.2 The first year of the epidemic

In 2007 the Q-fever outbreak was confined to a relatively small area. In July 2007, the Outbreak Management Team of the Netherlands decided to offer all pregnant women living in that area a screening test for Q-fever. This decision was based on the fact that a policy based on signs and or symptoms was not possible [58] as asymptomatic infections could carry the same risk for adverse pregnancy outcome and chronic infection as symptomatic cases. Testing of all pregnant women in outbreak situations was also common policy in other countries. In France, the recommendation was to treat pregnant women testing positive and for those testing negative, to repeat testing on a monthly basis until delivery [54]. Public health practitioners in the south of the Netherlands tried to identify all women who were pregnant or who had recently delivered in the affected area. They were contacted by letter and offered the test. Out of 29 women identified through midwives and obstetricians working in the area, 19 responded, were interviewed and underwent serological testing with IFA (Focus Diagnostics) in which a titre of 1:64 was considered positive. None of these women experienced or had experienced signs or symptoms of Q-fever. Two women however had serological evidence of a recent infection and one of an older infection [59]. The two women with serological evidence of recent infection were treated with cotrimoxazole for the duration of the pregnancy, as recommended in the literature [55]. Both delivered under strict hygiene measures and both pregnancies and deliveries were without complications. Birth products tested by PCR all were negative. In none of the neonates there was serological or PCR evidence of vertical transmission of Q-fever.

6.3 2008–2010

In the following years, the epidemic spread to a much larger geographical area with a population of almost two million people. This raised the question whether screening of pregnant women for acute Q-fever infection was necessary or feasible. The adverse effects from untreated Q-fever infections were compared with the possible side effects of long-term antibiotic treatment during pregnancy. In July 2008 an international meeting organized by the Centre for Infectious Disease Control and the Health Council of the Netherlands met to discuss the feasibility of screening all pregnant women for a recent Q-fever infection.

In all reported studies, there are a limited number of pregnant women with Q-fever for whom pregnancy outcomes (adverse or otherwise) have been reported (<100 women for all studies combined). Most reports concern retrospectively collected data, which don't allow quantification of the risk for an adverse outcome of an infection during pregnancy. Based

on this information and the fact that the epidemic had spread to a larger geographical area, the recommendation was that screening of all pregnant women for recent Q-fever was not recommended [60] by the Health Council of the Netherlands 2008. Several retrospective and prospective studies were set up in response to the urgent need for better quantification of the risk of adverse pregnancy outcome among pregnant women with acute Q-fever in early pregnancy.

6.4 A population-based retrospective follow-up study

In a retrospective study, the presence of antibodies against *C. burnetii* during pregnancy was determined by testing sera that had routinely been collected in the Prenatal Screening for Infectious Diseases and Erythrocyte Immunization (PSIE) programme (http://www.rivm.nl/pns_en/). This screening programme for hepatitis B, syphilis, and HIV is offered to all pregnant women in the Netherlands at around the 12th week of pregnancy. Samples were available in a high percentage of pregnancies as they are often stored for a period of 1 year after initial analysis. Sera were analysed using an IFA for detection of IgG and IgM antibodies. A recent infection was defined as the presence of anti-phase II IgM and anti-phase II IgG antibodies with a titre of ≥1:64. A possible infection was defined as a solitary IgM II ≥ 1:64 and a past infection as the presence of anti-phase I and II IgG antibodies without IgM being present. Information on pregnancy outcome was obtained from the Netherlands Perinatal Registry (PRN) – a database that represents the joint efforts of the professional organizations of midwives, gynaecologists, obstetrically-trained general practitioners and paediatricians in the Netherlands. The PRN contains perinatal data from 16 weeks of gestation onwards for 96% of all births in the Netherlands. It was estimated that 60% of pregnant women were included in the study during the study period, based on the registered number of births. In this study, almost 4.5% of women had a recent or past infection. The presence of antibodies against *C. burnetii* was not significantly associated with an adverse pregnancy outcome as measured by: preterm delivery (gestational age below 37 weeks), low birth weight <2,500 g, birth weight for gestational age <10th percentile, foetal or neonatal mortality, congenital malformation and 5-min Apgar score <7 [61].

6.5 A Prospective screen and treat study

In 2010 a clustered randomized controlled trial among pregnant women within the area of high transmission was started in the Netherlands [62]. The study participants were recruited by midwives in these high risk areas. The midwife centres were randomized to recruit pregnant women from the control group or the intervention group. When taking part in the intervention group, blood samples were taken and tested immediately for Q-fever. Patients were referred to a hospital for further pregnancy monitoring and long-term bacteriostatic treatment, if found positive for acute or chronic Q-fever. In the control arm, blood samples

were stored and analysed for Q-fever only after delivery. If tested positive for Q-fever after pregnancy, antibiotics were started if needed as part of regular health care. The objective of the study was to measure differences in obstetric or maternal complications in Q-fever positive women between the screened and control group. Because the outbreak of Q-fever in the Netherlands was successfully managed, relatively few pregnant women included in this study experienced a recent infection with *C. burnetii*. By September 2010, 815 samples had been examined, showing an overall seroprevalence of 15%, but with only 4% having a serologic profile suggesting recent infection [63]. The final results of this study are not yet available.

6.6 No evidence of adverse effects on pregnancy outcome in the Netherlands

Data from the literature on the effects of a Q-fever infection in pregnant women are limited. Currently the best available evidence with regard to adverse pregnancy outcomes comes from a large case series and from several case reports documenting one to two cases [55; 64; 67]. Case reports and case series have methodological limitations and selective publication of severe outcomes cannot be ruled out. In contrast, in the Dutch outbreak the presence of antibodies against *C. burnetii* in early pregnancy was not associated with adverse pregnancy outcome. This might be explained by a possible difference in pathogenicity of different bacterial strains or because we were not able to include early miscarriages in the study. We have to conclude that in the Dutch Q-fever outbreak, no evidence was found for adverse effects on pregnancy outcome among pregnant women with an asymptomatic Q-fever infection in early pregnancy. Based on this, there is insufficient basis for recommending large-scale screening of pregnant women in high incidence areas.

7. LONG-TERM EFFECTS OF ACUTE Q-FEVER

7.1 From acute to chronic illness

According to the literature, 60% of infected Q-fever patients are asymptomatic, while 20% of patients develop mild symptoms [68]. The remaining 20% present with more severe symptoms including high fever, severe headache, night sweating, nausea, diarrhoea, pneumonia, hepatitis, pericarditis, myocarditis, neuro- logical symptoms and weight loss [69]. The acute illness spontaneously resolves after 2–6 weeks [70]. However, the organism or its partly degraded remains can persist in bone marrow, which can cause future episodes. Chronic illness after acute Q-fever can express itself in different forms [71; 72]. Classic Q-fever endocarditis may take 10–15 years to develop and presents with cardiac vegetations that contain viable Coxiella bacteria. Recrudescent granulomatous infections can also occur. Patients with these two forms present with elevated levels of antibodies and persistent presence of viable *C. burnetii*. Another long-term effect of Q-fever is QFS (post-Q-fever fatigue syndrome). Con-

trary to the first two forms, QFS may present while there are no viable Coxiella and antibody levels are low or negligible. This is confusing for clinicians and patients alike.

7.2 Laboratory Diagnosis of Chronic Q-Fever

Acute Q-fever may develop into chronic Q-fever in 2% of patients, a potentially lethal disease with endocarditis as the main presentation [73]. Patients with previous cardiac valve pathology, aneurysms or vascular grafts, the immuno- compromised and women who are infected during pregnancy are at risk of chronic Q-fever [33]. An IFA IgG phase I antibody titre ≥1:800 is considered highly predictive for chronic Q-fever [40; 54; 74]. The final diagnosis of chronic Q-fever is made when a suspect serologic profile is combined with a positive PCR [75]. However, considerable uncertainties exist about the value of serology to identify chronic cases, and the value of a positive PCR is not completely clear. At the regional laboratory of Jeroen Bosch Hospital ('s-Hertogenbosch, the Netherlands), located at the epicentre of the Dutch outbreak, we evaluated the serologic profiles of 686 patients diagnosed with acute Q-fever in 2007 and 2008 at 3, 6 and 12 months after diagnosis [76]. Our results differ from data provided by others, as high IgG phase I antibody titres at a 3-month follow-up were not predictive for chronic Q-fever and IgG phase I antibody titres greater than IgG phase II antibody titres were rarely seen. An IgG phase I ≥1:1,024 at 6 months seemed to have the highest sensitivity for detecting chronic Q-fever, but the probability that cases with this profile actually had chronic Q-fever is low. Chronic Q-fever cases show a persistently high (≥1:1,024) or increasing IgG phase I antibody titre, combined with a persistently high (≥1:4,096) IgG phase II antibody titre. A serologic cut-off at ≥1:1,024 (or at the previously proposed ≥1:800) provides adequate sensitivity and positive predictive value. The study confirmed that IgG phase I is a good screening test, in our case with a cut-off of ≥1:1,024, at a follow- up of between 6 and 12 months after the acute Q-fever episode. A more stringent follow-up scheme is required for patients with clinical risk factors. Based on the experience gained since 2007, the serologic follow-up strategy is now one analysis at 9 months after an episode of acute Q-fever. For patients with specific risk factors, the serological follow-up strategy at 3, 6 and 12 months is maintained, combined with a PCR test. The diagnosis of chronic Q-fever and the decisions about treatment were made by a multidisciplinary team of medical specialists, based on serologic profile, PCR results, the presence of clinical risk factors, clinical presentation, and other patient characteristics. Of the 686 acute Q-fever cases that were followed up, 1.6% converted to a classic chronic case with microbiological evidence [76]. In the epidemic in the Netherlands, we found that the antibody titre of IgG phase I ≥1:1,024 is not useful for immuno- compromised patients and every follow-up serum sample must be tested by PCR independently of the serological profile. In endocarditis patients, we concluded that the PCR in a minority of patients is negative despite having vegetation's on echocardiography. Almost every vascular patient has a chronic serological profile and a positive PCR.

A Dutch consensus on chronic Q-fever was recently formulated [77]. A distinction is made between 'proven', 'probable', and 'possible' chronic Q-fever. Proven chronic Q-fever requires (1) a positive PCR in tissue or blood in the absence of an acute Q-fever infection; or (2) an IFA phase I IgG titre ≥1:1,024 and evidence of endocarditis; or (3) an IFA phase I IgG titre ≥1:1,024 and evidence of vascular infection by radiologic imaging.

7.3 Fatigue in Q-fever patients

Following acute Q-fever, up to 60% of patients may experience post-infection fatigue symptoms. These symptoms can persist for 6–12 months, after which they spontaneously resolve [78]. Post-infection fatigue also occurs after other infectious diseases such as Lyme disease [79]. In 10–15% of Q-fever patients, fatigue can last from 5 to 10 years [80] and is then often referred to as QFS, with a symptom presentation similar to chronic fatigue syndrome (CFS). Some studies state that cytokine deregulation and immuno- modulation due to the persistence of C. burnetii may be responsible for prolonged fatigue, but others contradict this [81]. An impaired or deregulated immune response or the long-term persistence of the bacteria or its antigens and the immune response may also play a role.

7.4 A typical Q-fever patient

'Jan Verkerk' is a 48-year-old self-employed male. He ran a small, family-owned bicycle shop and did most of the work himself. He was also an active sportsman, running 15 km three times a week and cycling daily. He had no known underlying physical or psychological diseases. In May 2007 he developed Q-fever and visited his general practitioner (GP) for the first time in years, presenting with high fever and pneumonia. These acute symptoms disappeared during ensuing weeks, but 1 year later and despite his best efforts, he still hadn't resumed running at his normal level. He was feeling constantly tired and was struggling to manage his business. He did not sleep well due to night sweating, was unable to concentrate, and suffered muscle and joint pains. He visited his GP many times, but several blood tests revealed nothing. He felt misunderstood by his GP, who seemed unable to help him, and he worried that if he did not recover he might not be able to manage his shop any longer. After speaking with other patients who told a similar story, he called the Department of Infectious Diseases of the Municipal Health Service to find out if this was a normal experience, whether others had similar problems, what further investigations could be done, and how he could be treated for his persisting symptoms.

7.5 The health status of Q-fever patients after Long-term follow-up

In response to the many signals and questions about persisting symptoms, particularly fatigue in Q-fever patients from the 2007 cohort, the collaborative multidisciplinary study Q-Quest I was started in 2008 [82]. A validated questionnaire, the Nijmegen Clinical Screen-

ing Instrument (NCSI), was used to obtain a detailed assessment of the health status in Q-fever patients 12–26 months after the onset of their illness. This study is the largest and longest follow-up study of Dutch Q-fever patients from the 2007 and 2008 outbreaks. In 2009, 870 Q-fever patients from the 2007 and 2008 outbreaks were asked to complete the questionnaire based on an empirical definition of health status [83], covering physiological functioning, symptoms, functional impairment and quality of life as the main domains. These domains were subdivided into eight sub-domains: subjective symptoms, dyspnoea emotions, fatigue, behavioural impairment, subjective impairment, general quality of life, health related quality of life, and satisfaction with relations [84]. We compared the NCSI scores of these Q-fever patients with normal data from healthy individuals and patients with severe chronic obstructive pulmonary disease (COPD).

Our findings demonstrate that in comparison to healthy individuals, Q-fever patients – especially those that were hospitalised – present 12 to 26 months after the onset of illness with more severe clinically relevant subjective symptoms, functional impairment and impaired quality of life. The long-term health status of two-thirds of Q-fever patients was severely affected for at least one sub-domain. Year of illness onset, level of education and smoking behaviour had no significant influence on sub-domain mean scores. Published data on the health status and its sub-domains of Q-fever patients are scarce. Hatchette *et al*. (2003) [85] reported that 52% of Q-fever patients were symptomatic and had an impaired quality of life 27 months after infection, using the 36-Item Short Form Health Survey (SF-36), with significantly lower scores, compared to non-infected controls in the domains of physical pain, function and role, emotional role and social function.

In Q-Quest I, the sub-domains 'general quality of life' and 'fatigue' measured with the NCSI were severely and clinically impaired, compared to the reference group. More than half, 59% of patients had abnormal (mild to severe) fatigue, similar to other publications, which indicate that 60% of patients reported protracted fatigue [68] and up to 69% fatigue [78] 5 years after infection. A small study on Dutch patients that measured a 1-year follow-up and also used the NCSI reported a higher rate of 53% of patients with severe fatigue [86], whereas the Q-Quest I study reported 44%.

The health status can be impaired after pneumonia regardless of the causative organism. Dutch pneumonia patients had significantly affected SF-36 scores 18 months after pneumonia on the subscales 'physical function' and 'general health status' [87]. Survivors of a Legionnaire's Disease outbreak in the Netherlands 17 months after infection reported severely impaired SF-36 domains: 'physical role function', 'general health' and 'vitality' [88]. Up to 75% of patients reported fatigue. In Q-Quest I hospitalization in the acute phase was significantly related to long-term behavioural impairment [82], poor health-related quality of life [82] and subjective symptoms [82]. Severity of initial illness generally has a negative influence on the long-term quality of life [89; 90]. Similarly, the severity of the acute Q-fever symptoms

predicts long-term symptoms [91]. Hospitalisation can be seen as an indicator of the severity of the initial infection. We conclude that Q-fever patients with severe acute illness are more likely to experience a long-term impaired quality of life. Lung or heart disease, depression and arthritis also significantly affected the long-term health status of Q-fever patients. Other authors state that underlying heart [92; 93] or lung disease [94], arthritis [95], depression [96] and diabetes [97] all have a negative effect on different sub-domains of the health status. In Q-Quest I this effect was also found for all underlying conditions, except for diabetes. It was not possible to compare data with existing studies as most of these studies focus on specific diseases (such as COPD) and grades of severity.

7.6 THE Q-FEVER PATIENT SOCIETY

In 2007 and 2008 the Q-fever outbreaks in the province of North Brabant did not receive much media attention. In 2009, the outbreaks expanded to a larger area outside Brabant and patient numbers rose to over 2,000. The number of patients presenting with long-term effects grew, the precautionary veterinary measures were stepped up and media attention increased as a result. This fed the public interest. Then, at the height of the Q-fever epidemic in 2009, most of the media attention switched to the influenza pandemic. Some general practitioners and other medical doctors and public health officials felt that the concurrent Q-fever outbreak received insufficient attention. At the same time, GPs and patients increasingly reported long-term complaints. In November 2009, with help and financial support from the Province of North Brabant, a Q-fever Patient's Society was founded. This society offers patients a platform to meet and express concerns and needs such as on treatment options.

Several hospitals now run Q-fever out-patient departments for follow-up of Q-fever patients but care in these centres is not standardized. In June 2010, the Patient's Society requested the Minister of Health to focus attention on patients with long-term complaints after acute Q-fever infection. The National Institute for Public Health and the Environment was asked to draft guidelines on the treatment of long-term complaints after acute Q-fever, and the product of a multidisciplinary working group is expected in 2012.

7.7 An opportunity for more research and understanding

Many questions on the late effects of Q-fever remain unanswered, such as the effectiveness of treatment of QFS [98] with cognitive behavioural treatment and graded exercise therapy. The outbreaks in the Netherlands offer a unique opportunity for prospective research (the Q-Quest II study) on the long-term health outcomes in Q-fever patients. With more than 4,000 acute Q-fever cases reported up to November 2010 and symptoms that can last for 10 years or more, a considerable burden of disease in coming years is expected for patients

and the affected communities. GPs and other medical doctors should be aware that Q-fever patients may present with long-term symptoms, especially if they have been hospitalised or have co-morbidity (heart or lung disease, or depression). Ongoing research on the treatment and recovery of Q-fever patients should offer a better understanding of the delayed and long-term effects of this zoonosis. There is a particular need for randomised clinical trials to test the effectiveness of treatment options.

8. Q-FEVER VACCINATION IN THE NETHERLANDS

8.1 Vaccination decisions during the Q-fever epidemic

The annual Q-fever epidemics that began in 2007 prompted Dutch policy makers to consider introducing a human vaccination programme to protect people at risk for severe outcomes of the disease. However, early live attenuated and sub-unit vaccines were abandoned because of low efficacy and safety concerns, leaving just one human Q-fever vaccine. This whole-cell vaccine was developed and registered in Australia and is licensed under the name Q-vax. It is not registered in the Netherlands or in any other European country. There were logistical and legal constraints to introducing a non-registered vaccine that required extensive testing of subjects before vaccination. Human vaccination can play no role in controlling the epidemic but the increasing number of reports of long-term effects in patients with chronic Q-fever eventually caused both professionals and decision makers to reconsider the introduction of the vaccine in the Netherlands. At the same time, hospitals and public health services were confronted with an increasing number of worried Q-fever patients, both acute and chronic, some of whom travelled to Australia at their own expense to be vaccinated. In 2010, the Government asked the Health Council of the Netherlands to advice on the possible use of the vaccine.

8.2 The Q-vax vaccine

Q-vax consists of formalin inactivated *C. burnetii* and was developed by CSL limited (CLS Biotherapies). It has been licensed in Australia to protect at-risk slaughterhouse employees and veterinary professionals [99]. In this respect, the vaccine was quite successful and is still in use [100; 101].

Analysis of the vaccine's efficacy in selected groups of professionals with a potentially high attack rate shows a protection rate of 97% [102]. Vaccinating subjects without a measurable immune response to *C. burnetii* is safe, but does commonly result in mild local reactions (33–48%) or mild systemic reactions (9%) such as headache [103]. Between 2002 and 2006, a large campaign in Australia saw the vaccination of 50,000 patients, resulting in eight serious adverse events requiring hospital admission and one life-threatening event. No deaths have

ever been recorded after vaccination [104]. It is noteworthy that this data comes from a specific group of young and predominantly healthy males, the vaccine is only given to subjects over 15 years of age, and it is not administered to pregnant women.

Data is not available on the effectiveness of the vaccine in persons other than healthy workers. Furthermore, the vaccine can only be given to those not previously in contact with *C. burnetii*, as vaccinating subjects that have already mounted an immunological response may lead to serious adverse reactions such as sterile abscesses and systemic symptoms of inflammation. To prevent this, serology and skin testing must be performed to identify those who have previously had contact with *C. burnetii*. Although these tests are not complicated per se, they can be difficult to organise and require specific skills such as administering and interpreting of the skin test. To further complicate matters, laboratory tests are not standardised, and different serologic tests systems and cut-off values are used.

8.3 Target Groups for Vaccination

Patients affected with Q-fever come mainly from specific areas in the south of the Netherlands. However, considerable differences occur within the affected area, and people living near affected farms may be especially affected. Nevertheless, localised mass vaccination has never been considered.

Preliminary data indicate that high numbers of professionals have been infected with *C. burnetii* – studies performed among goat and sheep farmers and veterinarians showed seroprevalence figures of up to 80%. Since the majority of these risk groups had already been exposed with a limited burden of disease, it was decided not to vaccinate them. However, those just starting out in a high-risk career, such as veterinarians, could be considered as candidates for vaccination.

The Q-fever vaccine could be of use for population groups with underlying disease that make them at risk for long-term effects. Although these long-term effects are quite rare, they can be very serious and include endocarditis and the infection of large blood vessels [74; 105]. The treatment of chronic Q-fever requires long-term (>1.5 years) antibiotic treatment and sometimes cardiovascular surgical interventions.

Patients with pathologic heart valves or blood vessels are particularly at risk. However, most of the studies in this area have been performed retrospectively and suffer from considerable selection bias. This means that the true contribution and magnitude of the risk associated with pre-existent factors is not known. It is also unclear whether minor valve or vessel pathology could develop into serious pathology during chronic Q-fever. Furthermore, little is known about the incubation period of serious long-term effects of chronic Q-fever.

Once the decision has been made to vaccinate patients at risk, these uncertainties matter and must be considered. For example, the screening of all acute Q-fever patients for heart defects with echocardiography (as advised in the international literature) was not feasible

during the large-scale Dutch outbreak [86; 105]. Similar screening options for aneurysms in a given population may also not be feasible.

For these reasons, defining and selecting patient groups for vaccination is not a simple matter. In 2010, the Health Council of the Netherlands (2010) [30] identified the following groups as eligible for vaccination:

- Patients who have had endocarditis in the past
- Patients with artificial heart valves
- Patients with significant congenital heart anomalies, including those that required repair with
- Patients with structural defects of the aortic or mitral valve
- Patients with known aneurysm of the aorta
- Patients with vascular grafts
- Patients with severe peripheral vascular disease (such as Buerger's disease).

8.4 Deciding to vaccinate

Even though the use of the vaccine in certain groups has been advocated, this vaccine is not licensed in the Netherlands and its administration will not be part of a nationally steered programme. However, it is considered part of health care under the responsibility of the treating physician. Together with the patient, the physician must weigh the potential benefits and disadvantages of vaccine administration. These decisions need to be made with full awareness of the medical and the epidemiological risks involved.

Vaccine administration can only be carried out after a professional skin test reading and serology result analysis. This requires a standardised process with similar cut-off titres and specificity tests, as well as centralised vaccination to realise standardised quality of care. Therefore, even though the vaccine has not been added to the national vaccine programme, its introduction in 2011 was coordinated by the National Institute of Public Health and the Environment, in collaboration with a commercial partner, regional public health departments and local physicians. In the vaccination campaign, early 2011, 1,354 people were vaccinated, all from the defined high risk groups.

CONCLUSIONS

Between 2007 and 2009, the Netherlands experienced an unprecedented series of seasonal outbreaks of Q-fever. Dairy goats are clearly implicated in these outbreaks. In 2010 there were a much lower number of notified acute Q-fever cases than in 2009, probably due to the drastic veterinary interventions such as culling of pregnant goats on infected farms, vaccination, and hygiene measures. But the risk of Q-fever outbreaks and possibly other zoonotic

diseases remains high because of the cohabitation of 2.4 million inhabitants with 6.4 million animals in the province of North Brabant. A great deal of knowledge has been generated in the past few years but many questions remain. Ongoing research, including 20 PhD projects, is expected to significantly advance the knowledge base. Attention is now shifting from acute Q-fever to the problem of long-term effects of Q-fever, the extent of which is not yet known and which poses important challenges for diagnosis and treatment.

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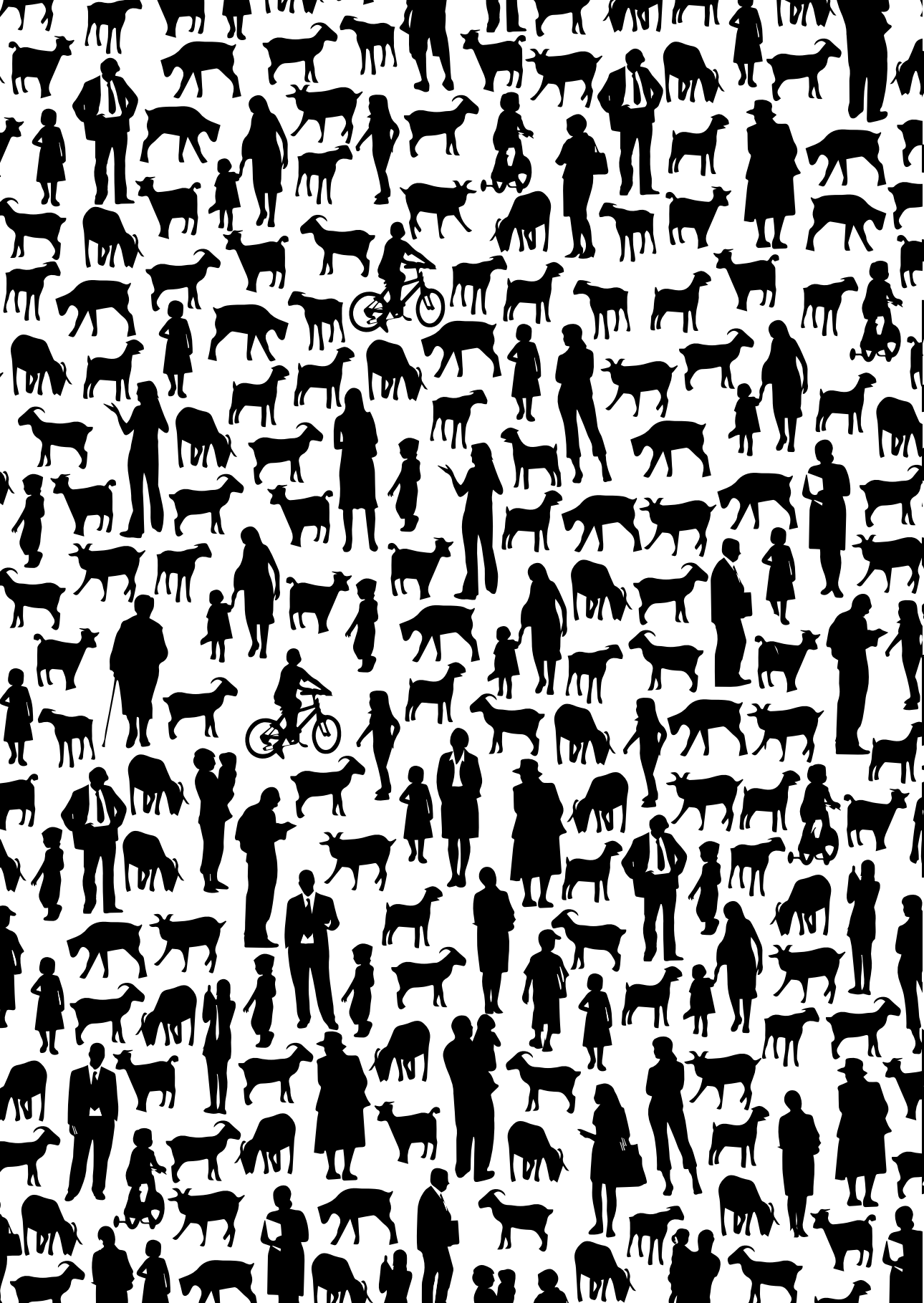
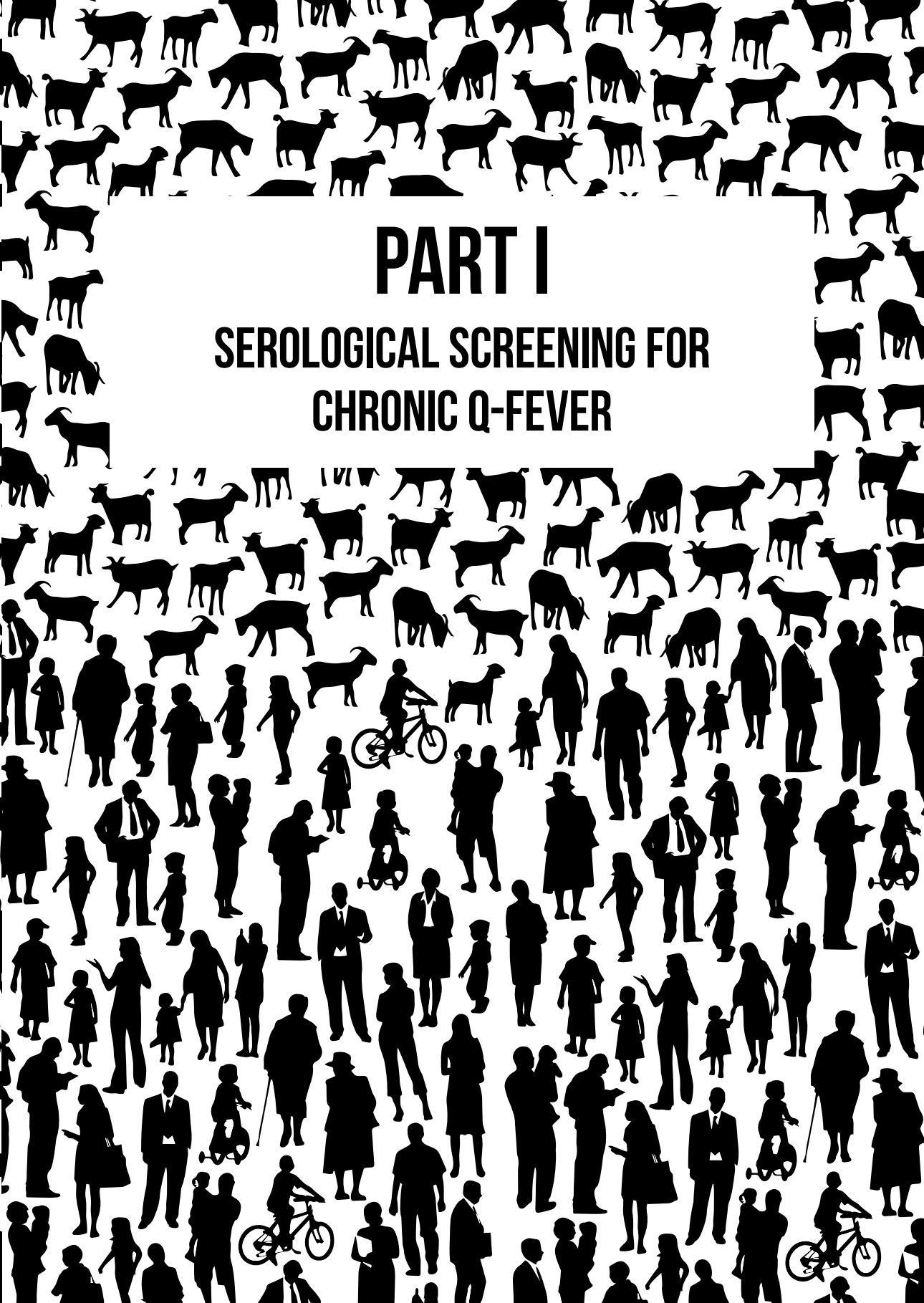
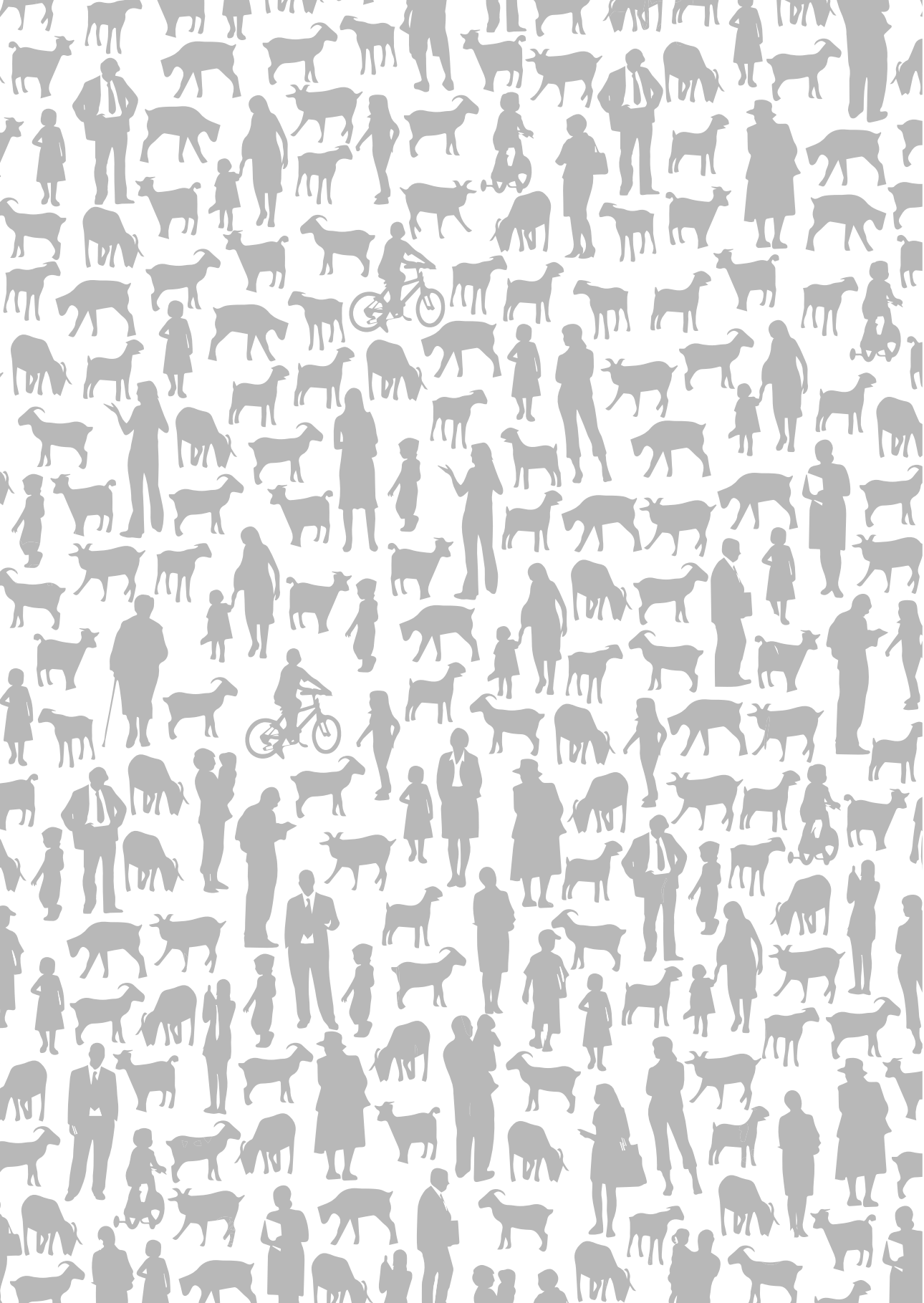




PART I

SEROLOGICAL SCREENING FOR CHRONIC Q-FEVER



Chapter 3

LARGE REGIONAL DIFFERENCES IN SEROLOGICAL FOLLOW-UP OF Q-FEVER PATIENTS IN THE NETHERLANDS

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ABSTRACT

Background

During the Dutch Q-fever epidemic more than 4,000 Q-fever cases were notified. This provided logistical challenges for the organisation of serological follow-up, which is considered mandatory for early detection of chronic infection. The aim of this study was to investigate the proportion of acute Q-fever patients that received serological follow-up, and to identify regional differences in follow-up rates and contributing factors, such as knowledge of medical practitioners.

Methods

Serological datasets of Q-fever patients diagnosed between 2007 and 2009 (n=3,198) were obtained from three Laboratories of Medical Microbiology (LMM) in the province of Noord-Brabant. One LMM offered an active follow-up service by approaching patients; the other two only tested on physician's request. The medical microbiologist in charge of each LMM was interviewed. In December 2011, 240 general practices and 112 medical specialists received questionnaires on their knowledge and practices regarding the serological follow-up of Q-fever patients.

Results

Ninety-five percent (2,226/2,346) of the Q-fever patients diagnosed at the LMM with a follow-up service received at least one serological follow-up within 15 months of diagnosis. For those diagnosed at a LMM without this service, this was 25% (218/852) (OR 54, 95% CI: 43–67). Although 80% (162/203) of all medical practitioners with Q-fever patients reported informing patients of the importance of serological follow-up, 33% (67/203) never requested it.

Conclusions

Regional differences in follow-up are substantial and range from 25% to 95%. In areas with a low follow-up rate the proportion of missed chronic Q-fever is potentially higher than in areas with a high follow-up rate. Medical practitioners lack knowledge regarding the need, timing and implementation of serological follow-up, which contributes to patients receiving incorrect or no follow-up. Therefore, this information should be incorporated in national guidelines and patient information forms.

INTRODUCTION

In the Netherlands, more than 4,000 patients were notified with acute Q-fever during seasonal outbreaks between 2007 and 2010 [1, 2]. However, at least ten times as many people might have been infected with *Coxiella burnetii* in this period and had either asymptomatic or non-diagnosed infections [3, 4]. Acute Q-fever may progress to chronic Q-fever in about 2% of cases [5]. Chronic Q-fever is not notifiable. There are no estimates for the proportion of asymptomatic acute *C. burnetii* infections that develop into chronic infection. The most common presentations of chronic Q-fever are endocarditis and vascular infections, conditions with high morbidity and mortality [6]. The diagnosis of chronic Q-fever is based on clinical presentation, presence of risk factors, diagnostic imaging techniques, detection of *C. burnetii* DNA in blood or tissue, and serological test results. Detection of an IgG antibody titre against phase I of *C. burnetii* of ≥1:1,024 in a commercially available immunofluorescence assay during follow-up screening is considered an important marker of chronic infection [7]. Serological follow-up of acute Q-fever patients is advised in order to identify and ensure timely treatment of chronic Q-fever [8–10]. Follow-up is especially important for patients with valvulopathy, vascular prosthesis/abnormalities, pregnant women, and immunocompromised patients, as they have a higher risk of developing chronic Q-fever after acute infection [9, 11].

A common but non-validated recommendation in the international literature was to offer all patients at least two serologic tests (at three and six months) in the first year after the diagnosis of acute Q-fever [12, 13]. In 2008 the advice to test all Q-fever patients at three, six, and twelve months after diagnosis was published in a Dutch microbiology journal [10]. Two years later, in 2010, new advice was published in another Dutch medical journal proposing one follow-up serologic test at nine months for low-risk patients, while the recommendation for high-risk patients was to test at three, six, nine, and twelve months [7]. During the Dutch Q-fever epidemic, apart from these recommendations in scientific journal articles, there were no national guidelines on the serological follow-up of Q-fever patients.

In the province of Noord-Brabant, one Laboratory of Medical Microbiology (LMM) used an automatic patient recall system for the serological follow-up of patients with acute Q-fever. The other two LMMs depended on medical practitioners to request serological Q-fever follow-up. The Municipal Health Service (MHS) Hart voor Brabant received information from both patients and health professionals that indicated poor serological follow-up of Q-fever patients with regional differences. Therefore the question arose, if and to what extent the serological follow-up rates of Q-fever patients differed per LMM catchment area. Are chronic Q-fever cases potentially missed due to a lack of proper follow-up? The aim of this study was to investigate the extent to which acute Q-fever patients received serological follow-up, identify regional differences and contributing factors and study the differences in knowledge and practices regarding serological follow-up among medical practitioners.

MATERIALS AND METHODS

Ethics Statement

According to Dutch legislation, written consent from patients for the use of anonymized information from laboratory databases is not necessary; therefore ethical review was not required.

Study population and data collection

Laboratories of Medical Microbiology (LMMs)

Three LMMs (A, B, and C, see Figure 1) performed the majority of Q-fever serology in the province of Brabant. LMM-A in 's-Hertogenbosch provided active follow-up by contacting every diagnosed Q-fever patient for serological follow-up through an automated system. All patients received an explanatory letter and a laboratory form. The other two LMMs, LMM-B in Tilburg and LMM-C in Veldhoven, performed serological follow-up only upon request of a medical practitioner.

All three LMMs provided anonymous serological datasets from all patients that were diagnosed with acute Q-fever between January 2007 and December 2009. Follow-up samples up to 15 months after diagnosis of Q-fever were analysed for timing and frequency. Samples that were taken within 60 days of diagnosis were not considered as follow-up samples. Follow-up periods were divided into 60–135 days (2–4.5 months), 136–255 days (4.5–8.5 months) and 256–450 days (8.5–15 months) in order to include the three-, six-, and twelve-month follow-up, respectively. The nine-month follow-up started in 2010; therefore these data are not presented as a separate follow-up moment in this study but are included in the follow-up period 256–450 days (8.5–15 months). Patients that were present in the dataset of more than one LMM were only included once by checking gender, date of birth and the postal code. These patients were then allocated to the LMM that requested the Q-fever serology. We conducted semi-structured interviews with the head medical microbiologist of each laboratory regarding perceived role and responsibility of serological follow-up of Q-fever patients.

Information from general practitioners and medical specialists

In December 2011, questionnaires were posted to all 240 general practices (with 501 general practitioners) and all internists (n=42), cardiologists (n=46), and pulmonologists (n=24) from all hospitals (n=6) in the MHS region Hart voor Brabant (MHS HvB), the epicentre of the Q-fever epidemic (see Figure 1). We used the term medical practitioners to refer to both general practitioners (GPs) and medical specialists. Non-responders received a reminder after two and four weeks. Reminders were not sent to GPs when one out of three GPs from the medical practice responded.

The questions posed were: work location (postal code), LMM used, the number of Q-fever patients treated and the knowledge and practices regarding serological follow-up of Q-fever patients. Practice questions included informing the patient about the importance of serological follow-up (never/sometimes/often/always); requesting Q-fever follow-up serology for patients (never/sometimes/often/always); and differentiating between high- and low-risk patient groups when offering follow-up (never/sometimes/often/always). Never and sometimes were regarded as inadequate practice. Knowledge questions (multiple-choice) focused on identification of high-risk groups for developing chronic Q-fever i.e., "people with valvulopathy, vascular prosthesis/ abnormalities, pregnant women, and the immunocompromised". The possibility to add another perceived risk group was offered as an open question. The same method was used for the follow-up, timing and differences in follow-up between high- and low-risk group patients. Not being able to identify three high-risk groups, and making no distinction in frequency or timing of serological follow-up between high- and low-risk groups were regarded as incorrect answers.

Medical practitioners were divided in groups with zero, few (≤10) and many (>10) Q-fever patients and the Q-fever incidence area where they worked. These Q-fever incidence areas were based on the cumulative Q-fever notification data from 2007 up to December 2010 in the area of the MHS HvB and were defined as low (<150 cases per 100,000 residents), medium (150–300/100,000) and high (>300 up to 2,425/100,000) (see Figure 1).

Data analysis

All data were analysed using SPSS Statistics version 19.0.0 (SPSS Inc.). Proportions were compared with the Mantel-Haenszel chi-square and Fisher's exact test. *P*-values were based on two-tailed tests, defining $p<0.05$ as significant.

RESULTS

Laboratories of Medical Microbiology

We received serological datasets of 3,198 patients diagnosed by three LMMS between 2007 and 2009 with serology indicative of acute Q-fever (Figure 1). The difference in percentage of patients without serological follow-up within 15 months of diagnosis, differed greatly between LMMs with an active or passive follow-up approach (Table 1); 5% (120/2,346) versus 74% (634/852) respectively (OR 54, 95% CI: 43–67). The percentage of patients that did not receive serological follow-up was comparable for the two LMMs without active follow-up (74%). Overall, 24% (754/3,198) of Q-fever patients did not receive any follow-up.

During the interviews, one of the heads of an LMM (without a follow-up service) stated that both the medical practitioner and the MHS were responsible for the serological follow-up

of Q-fever patients. The other two microbiologists perceived this to be a shared responsibility between medical practitioners, patients, and the LMM. The microbiologist in charge of LMM-A, the LMM that provided active follow-up, chose a proactive approach at the beginning of the epidemic. The heads of the two LMMs without active follow-up stated that in their opinion an active recall of patients by an LMM was not an option because they regarded this as interfering with the responsibility of the medical practitioner.

Response questionnaires and interviews medical practitioners

The response rate of general practices was 70% (167/240), and included 42% (209/501) of GPs. The response rate of specialists was 29% (32/112); highest for pulmonologists 37% (9/24) and internists 33% (14/42), and lowest for cardiologists 15% (6/46). The most frequently mentioned reasons for not participating in the study by non-responders who gave reasons (n=70) were no Q-fever patients (38%) or time constraints (25%).

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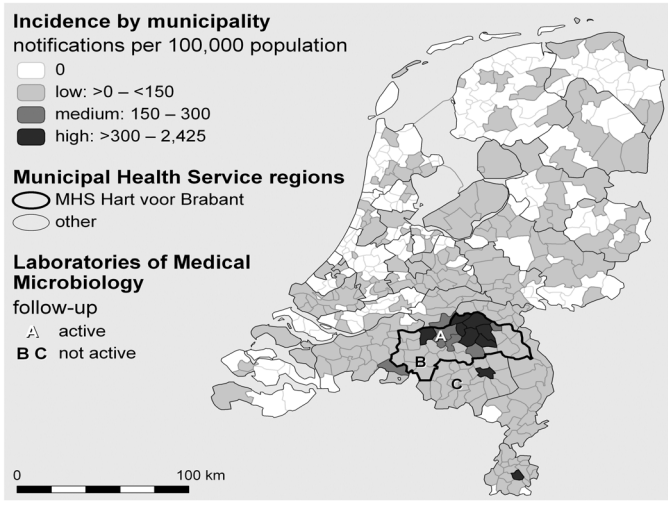

Figure 1. Cumulative Q-fever incidence in the Netherlands from 2007 up to and including 2010, marking the Municipal Health Service regions, highlighting the Municipal Health Service region Hart voor Brabant and the Laboratories of Medical Microbiology, A in 's-Hertogenbosch, B in Tilburg, and C in Veldhoven.

Table 1. Diagnosis and serological follow-up up to 15 months (450 days) after diagnosis of Q-fever for three Laboratories of Medical Microbiology (LMM).

	Provision follow-up service and location LMM			
	Yes	No	No	Total
	's-Hertogenbosch	Veldhoven	Tilburg	All LMM
	n *(%)*	n *(%)*	n *(%)*	n *(%)*
Total diagnosis Q-fever	2,346 *(100)*	527 *(100)*	325 *(100)*	3,198 *(100)*
Diagnosis by				
GP	1,786 *(76.2)*	320 *(60.7)*	91 *(28.0)*	2,197 *(68.7)*
Specialist	536 *(22.8)*	207 *(39.3)*	137 *(42.1)*	880 *(27.5)*
Unspecified	24 *(1.0)*	0 *(0.0)*	97 *(29.8)*	121 *(3.8)*
No follow-up	120 *(5.1)*	392 *(74.4)*	242 *(74.5)*	754 *(23.6)*
Received follow-up in days after diagnosis				
60–135 [a]	2,077 *(88.5)*	67 *(12.7)*	47 *(14.5)*	2,191 *(68.5)*
136–255	2,015 *(85.9)*	57 *(10.8)*	40 *(12.3)*	2,112 *(66.0)*
256–450	1,926 *(82.1)*	61 *(11.6)*	24 *(7.4)*	2,011 *(62.9)*
Follow-up requested by				
GP	NA	86 *(46.5)*	43 *(43.9)*	129 *(45.6)*
Specialist	NA	99 *(53.5)*	55 *(56.1)*	154 *(54.4)*
Total	NA	185 *(100)*	98 *(100)*[b]	283 *(100)*

GP: general practitioner; LMM: Laboratory of Medical Microbiology; NA: not applicable.

[a] A sample taken within 60 days after diagnosis was not considered as a follow-up sample.

[b] For 13 samples the applicant was unknown (request by an external laboratory).

Knowledge and behaviour of medical practitioners regarding serological follow-up

Although 80% (162/203) of all medical practitioners with Q-fever patients reported informing patients of the importance of serological follow-up, 33% (67/203) stated never to request follow-up. Information on knowledge and practice questions for medical practitioners with Q-fever patients that do (sometimes/often/always) offer follow-up is provided in Table 2. Outcomes were comparable for different incidence areas and type of medical practitioner (GP or medical specialist). Medical practitioners with one to five Q-fever patients (mainly found in the low and middle incidence areas) seemed less likely to request serological follow-up, as 47% (27/58) stated never. There was no significant difference compared to those with more patients. Overall, there was no difference in reported practice of requesting follow-up serology between GPs in an area with or without an automatic recall-system (Table 3). GPs with many patients (>10) and working in the catchment area of a LMM without active follow-up requested follow-up significantly more often than those with few patients (≤10).

The ability to differentiate between high- and low-risk patient groups was comparable for GPs and specialists. The knowledge question; "are patients with a heart valve defect a high-risk group for chronic Q-fever" was answered 'yes' by 88% of GPs and 100% of specialists. For stents and vascular abnormalities this was 85% and 86%, for the immune compromised 85% and 79%, and for pregnant during the initial infection 74% and 61%, respectively. When looking at individual medical practitioners, 67% correctly identified all high-risk groups. When offering serological follow-up, 35% of GPs and 22% of medical specialists never consider the risk category of the patient. Medical practitioners with many (>10) patients scored significantly worse for identification of the correct high-risk groups, discussing the importance of serological follow-up with the patient, and requesting follow-up serology for high-risk groups (Table 2).

Both GPs (63%) and specialists (45%) assumed that the LMM requests follow-up. GPs with few Q-fever patients indicated that they were not acquainted with the procedure and referred patients to specialists. The main reason for not requesting serological follow-up, mentioned by GPs with many Q-fever patient cases, was the assumption that the LMM or the MHS would take this responsibility.

Table 2. Answers to knowledge and practice questions of medical practitioners (MPs) comparing those with few (≤10) and many (>10) Q-fever patients.

	Number of Q-fever patients per medical practitioner[a]						
	>10		**≤10**		**Total**		
	Answered Yes	**Total MPs**	**Answered Yes**	**Total MPs**	**Answered Yes**	**Total MPs**	**OR (95% CI)**
	n *(%)*	**n (100%)**	**n *(%)***	**n (100%)**	**n *(%)***	**n (100%)**	
Knowledge questions							
Makes distinction of risk groups for chronic infection	35 *(50.7)*	69 *(100)*	33 *(53.2)*	62 *(100)*	68 *(51.9)*	131 *(100)*	0.9 (0.4–1.8)
Identifies all high-risk groups for chronic infection	28 *(41.1)*	68 *(100)*	16 *(24.6)*	65 *(100)*	44 *(33.1)*	133 *(100)*	2.1 (1.0–4.5)
Practice questions							
Discusses importance of follow-up with patient	66 *(94.2)*	70 *(100)*	55 *(82.1)*	67 *(100)*	121 *(88.3)*	137 *(100)*	3.6 (1.1–11.8)
Requests follow-up Q-fever patients without distinction of risk groups	32 *(45.7)*	70 *(100)*	31 *(49.2)*	63 *(100)*	63 *(47.4)*	133 *(100)*	0.8 (0.4–1.7)
Requests serology at least once for low-risk groups	34 *(52.2)*	65 *(100)*	36 *(59.0)*	61 *(100)*	65 *(51.5)*	126 *(100)*	0.7 (0.4–1.5)
Requests serology at least three times for high-risk groups	34 *(57.6)*	59 *(100)*	18 *(30.5)*	59 *(100)*	52 *(44.1)*	118 *(100)*	3.3 (1.4–5.0)

95% CI: confidence interval; MPs: medical practitioners; OR: odds ratio.[a] Excluded are medical practitioners without Q-fever patients (n=30), those who never request serological follow-up (n=70) or gave not applicable (NA) answers.

Table 3. Regional differences in reported serological follow-up practices by GPs in regions with a Laboratory of Medical Microbiology (LMM) with or without an automatic follow-up system.

	Number of GPs by LMM region							
	LMM with automatic follow-up[a]; GPs n=123 (100%)				LMM without automatic follow-up[B]; GPs n=47 (100%)			
	Few patients ≤10	Many patients >10	Total	OR (CI)	Few patients ≤10	Many patients >10	Total	OR (95% CI)
	n *(%)*	n *(%)*	n *(%)*		n *(%)*	n *(%)*	n *(%)*	
Frequency serology request GP				0.6 (0.2–1.2)				4.8 (1.1–22.1)
Mostly/always	23 *(44.2)*	22 *(30.9)*	45 *(36.6)*		12 *(32.4)*	7 *(70.0)*	19 *(40.4)*	
Sometimes/ never	29 *(55.8)*	49 *(69.1)*	78 *(63.4)*		25 *(67.6)*	3 *(30.0)*	28 *(59.6)*	
Total	52 *(100)*	71 *(100)*	123 *(100)*		37 *(100)*	10 *(100)*	47 *(100)*	

95% CI: 95% confidence interval; GPs: general practitioners; LMM: Laboratory of Medical Microbiology; OR: odds ratio.

[a] Municipalities in the service area of a LMM with follow-up: Heusden, Oss, Maasdonk, Uden, Bernheze, Lith, Landerd, Vught, 's-Hertogenbosch (Den Bosch), Sint Michielsgestel, Veghel, Schijndel, Boekel, Boxtel.

[B] Municipalities in the service area of a LMM without follow-up: Dongen, Waalwijk, Tilburg, Oisterwijk, Gilze Rijen, Loon op Zand, Sint Oedenrode, Cuijk, Boxmeer, Mill en Sint Hubert, Hilvarenbeek, Sint Anthonis, Haaren, Grave.

DISCUSSION

Laboratory follow-up

After diagnosing acute Q-fever, serologic follow-up is considered essential for early detection and treatment of chronic Q-fever. During the Dutch Q-fever epidemic there was no national consensus or guidelines on serological follow-up of acute Q-fever patients. In an attempt to comply with the changing recommendations, LMMs and clinicians improvised. This led to an active recall of patients by one LMM, while in other regions medical practitioners had to organise this follow-up themselves. In this study we analysed the outcome of these two approaches. An active follow-up approach by a LMM led to a much higher follow-up rate compared to follow-up by medical practitioners only (OR 54, 95% CI: 43–67). When the responsibility of follow-up lies with medical practitioners, the outcome is poor. Overall, 1,187 (37%) patients received incomplete or no (24%; n=754) follow-up. Ideally, the percentage of chronic Q-fever cases found in the group of patients that did receive follow-up would be known, based on the conversion rate to chronic Q-fever. However, the diagnosis of chronic Q-fever is a combination of; an IgG phase I antibody titre against *C. burnetii* of ≥1:1,024 in immunofluorescence assay in a follow-up sample [7], the detection of *C. burnetii* DNA in blood or tissue, clinical findings, the presence of risk factors, and diagnostic imaging techniques. This additional information was unavailable. Chronic Q-fever is not notifiable and therefore we lacked accurate data on the occurrence of chronic Q-fever. We were unable to retrieve accurate data on chronic Q-fever from patients that were lost to follow-up, as patient's personal details were removed from the LMM database

for reasons of anonymity. We do however know that up to the beginning of 2013 a total of 3% (71/2,226) of patients of the LMM that provided active follow-up service had an antibody response (IgG phase I) suspect for a possible, probable or proven chronic Q-fever (personal communication, unpublished data Nicole H.M. Renders, Medical Microbiologist). However, new chronic cases are still being identified, as the average incubation period of chronic Q-fever may be long and definitive identification and characterization of chronic Q-fever patients is complicated. Based on an estimated 1–5% conversion rate to chronic Q-fever, we calculate that approximately 12 to 59 (1–5% of 1,187 patients without or with incomplete follow-up) chronic Q-fever patients might have been missed because of inadequate follow-up. Now that it is known that this many traceable patients received no or improper follow-up, the discussion arises whether offering serological testing years after the initial infection would be beneficial to patients. At the same time the current screening recommendations [14] are questioned. What percentage of chronic Q-fever might we expect to find per risk category and how should these categories be defined? Should all 1,187 Q-fever patients need to be recalled or only a selection of high-risk patients? What percentage of chronic Q-fever patients diagnosed several years after acute Q-fever would justify such a recall? Should one incorporate a time limit for follow-up for patients after an acute infection that do not belong to a risk category? Other important issues are the cut-off value of the immunofluorescence assay, and the duration and frequency of follow-up. In the Netherlands, several follow-up studies are currently being conducted that may answer some of these questions.

One would assume that patient compliance is the same regardless of the system. However, computer generated systems are known to improve patient compliance [15] and a diagnosis of acute Q-fever made by a laboratory with an active recall-system provides the best guarantee for receiving follow-up. The downsides of such a system are the unnecessary exposure of patients to blood tests and the overburdening of laboratory facilities. To prevent overburdening, the LMM needs clinical information from the medical practitioner to distinguish between acute and old infections [16] and risk categories, but this information is often not provided.

Response rate, knowledge and practices of medical practitioners

The response rate of the general practices was good (70%), and we consider our sample to be representative for GPs in the MHS region as the proportions of responding practices were comparable for the different incidence areas. We used the number of Q-fever patients per GP rather than incidence area because all GPs stated the number of Q-fever patients.

Approximately half of the medical practitioners lacked knowledge on high-risk groups, distinction between low- and high-risk patients, and the need to request serological follow-up for all acute Q-fever patients. A high proportion of medical practitioners (88%) reported that they discussed the importance of serological follow-up with the patient but it might be that an expected correct answer was given [17].

Barriers to behavioural change by GPs' and specialists' relate to knowledge, attitude and external factors [18, 19]. Although many different parties play a role in serological follow-up, correct information and knowledge [19] is the first step to compliance. During the epidemic, the MHS HvB regularly advised medical practitioners to contact a microbiologist for specific advice on follow-up and dispersed general information on the importance of follow-up in update letters and in every notification report letter (following the notification of a Q-fever patient). LMM-A and LMM-C mentioned the required serological follow-up on each Q-fever positive laboratory report while LMM-B discussed this with the medical practitioner by telephone. The lack of knowledge amongst medical practitioners may be due to a combination of changing recommendations on Q-fever follow-up [10, 12–14] combined with a lack of national guidelines (to this date) and general information overload [20].

Conclusion and recommendations

The serological follow-up of Q-fever patients poses logistical challenges. Our results clearly indicate that a LMM based follow-up system with active patient approach achieves high patient compliance compared with systems that rely on referral by medical practitioners. Also, the current registration systems of medical practitioners are not suited to follow-up Q-fever patients. Medical practitioners hold others, including the patient, responsible for follow-up and often lack knowledge on the indication for and implementation of serological follow-up of Q-fever. A lesson learned from this epidemic, is that recommendations on best practices regarding the serological follow-up of acute Q-fever patients should be translated into practical guidelines for medical practitioners early on during an epidemic. The recommendation on serological follow-up should also be incorporated in patient information leaflets. Recalling selected high risk patients that received incomplete or no serological follow-up should be considered. Additional information, on conversion to chronic Q-fever per patient category in time, is needed in order to decide which patient groups should be recalled and up to what time after initial infection. Organising such a recall needs to be a joint action by medical practitioners, the LMM, the Q-fever patient association and the MHS.

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was compiled by Ben Bom, of the National Institute for Public Health and the Environment, Bilthoven, the Netherlands.

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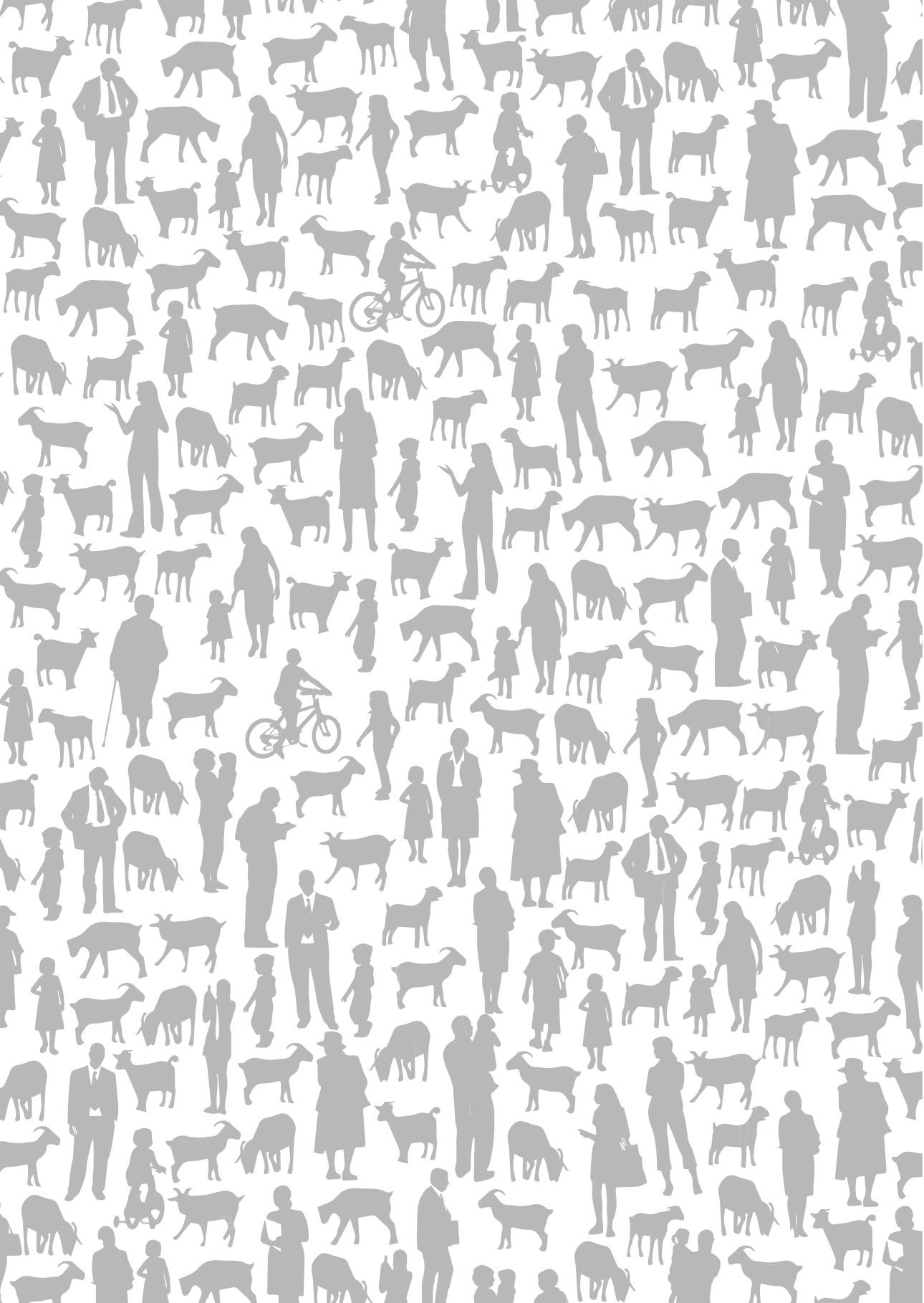

Chapter 4

STRATEGIES FOR EARLY DETECTION OF CHRONIC Q-FEVER: A SYSTEMATIC REVIEW

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ABSTRACT

Background

Chronic Q-fever, a condition with high morbidity and mortality, may develop after an acute infection with *Coxiella burnetii* (acute Q-fever). Several strategies have been suggested for early detection of chronic Q-fever, focusing on follow-up of known acute Q-fever patients and detection of asymptomatic or unknown chronic infections. As there is no international standard or consensus, the aims of this study were to summarise the available literature and assess the evidence for different follow-up and screening strategies.

Design

We conducted a systematic review by searching PubMed and Embase. Twenty articles were included, of which fourteen only provided information on follow-up of known acute Q-fever cases, four presented data on identification of previously unknown *C. burnetii* infections, and two had information on both topics.

Results

The conversion rate of acute to chronic Q-fever ranged from 0.0% to 5.0%. Most studies advised serological follow-up of acute Q-fever patients, but without consistent advice on optimum timing and duration. The recommendation to use echocardiography for all acute Q-fever patients to detect valvular damage remains controversial. Screening of high-risk patients in an outbreak setting is advised by studies investigating such a strategy.

Conclusions

There is sufficient evidence to support serological follow-up of all known acute Q-fever patients at least once during the first year following the acute infection, and more frequently in patients with known risk factors for chronic disease, such as heart valve- or vascular prosthesis. Screening of risk groups should be considered in outbreaks of Q-fever.

INTRODUCTION

Q-fever is a zoonotic disease caused by the intracellular bacterium *Coxiella burnetii* [1]. The acute infection can remain asymptomatic or present as a flu-like illness, pneumonia or hepatitis [1, 2]. Approximately 2% of symptomatic acute Q-fever cases progress to chronic Q-fever [3], a potentially lethal disease that can become apparent years after initial infection [4]. Most at risk for a chronic infection are patients with pre-existing valvular disease, aneurysms, vascular grafts, immunocompromised patients, and pregnant women [1]. The most common presentations of chronic Q-fever are endocarditis and vascular infections [5, 6].

C. burnetii has two antigenic phases: antibodies against phase II antigens (IgG phase II) predominate during acute Q-fever, whereas persisting high titres of IgG antibodies against phase I antigens (IgG phase I) are indicative for chronic Q-fever [7–10].

As chronic Q-fever has a high morbidity and mortality, early detection and treatment is important. Therefore, serological follow-up after an acute Q-fever infection is advocated to identify patients, although criteria for diagnosing chronic Q-fever are poorly defined. However, as most acute *C. burnetii* infections remain undetected, patients at risk for a chronic infection are unaware of their risk. In addition, determining the moment of the acute Q-fever infection is hampered by non-specific clinical symptoms and the limited accuracy of laboratory tests due to the long-term persistence of IgM phase II antibodies [11].

The main strategies to identify patients with chronic Q-fever infection are serological follow-up of known acute Q-fever patients and detection of asymptomatic or unknown infections [3, 12–16]. Furthermore, echocardiography is sometimes recommended to exclude hitherto unknown heart valve disease [2, 3, 17, 18]. To detect asymptomatic or unknown *C. burnetii* infections, patients at high risk for chronic Q-fever can be screened by serological testing [3, 8, 10, 16, 19–21] or a general population study can be performed in an outbreak area. Other issues that need to be considered are inclusion criteria for those at risk, frequency, optimum timing, intervals and duration of follow-up after diagnosis, analysis of risk factors, and serological and clinical case definitions of chronic cases. These decisions may depend on epidemiological criteria, such as epidemic versus endemic situation, and the number of exposed persons at risk for developing chronic Q-fever. Here, we review the strategies for early identification of chronic Q-fever infections as published in the international literature.

DESIGN

Search strategy and selection criteria

Relevant articles were identified by a systematic literature search of two major scientific databases, PubMed and Embase. Table 1 shows the search strategies used per database.

Search terms were categorised into; Q-fever; chronic disease; and follow-up/screening (Table 1). Terms referring to cost-effectiveness were also included. No limits were used for year of publication or language. Case reports were excluded in the search strings.

In selection step 1, abstracts and titles retrieved from the search strategies were independently assessed by two investigators (CW and WvdH).

Table 1. Search strategy used in PubMed and Embase.

Search string	**PubMed search terms**
Q fever	((Q fever[Mesh]) OR (coxiella burnetii[Mesh]) OR (Q fever[tw]) OR (coxiella[tw]) OR (Q-fever[tw]) OR (rickettsia burnetii[tw]) OR (rickettsia burnetii infection[tw]) OR (rickettsia burnetti[tw]) OR (rickettsiosis infection[tw]) OR (rickettsiosis rickettsia[tw]) OR (australian Q fever[tw]))
	AND
Chronic disease	((Chronic Disease[Mesh]) OR (chronic[tw]))
	AND
Follow-up/screening	((Follow-up Studies[Mesh]) OR (follow-up[tw]) OR (follow up[tw]) OR (screening[tw]) OR (screen*[tw]) OR (identif*[tw]) OR (reexaminat*[tw]) OR (long-term[tw]) OR (long term[tw]) OR (review[tw]) OR (strateg*[tw]) OR (check*[tw]) OR (general population[tw]) OR (population-based[tw]) OR (population based[tw]) OR (costs*[tw]) OR (cost effect*[tw]) OR (cost-effect*[tw]) OR (Cost-Benefit Analysis[Mesh]))
	NOT
Case reports	(case study) OR (case studies) OR (case report*)
	Embase search terms
Q fever	(exp Q fever/ OR exp Coxiella burnetii/ OR exp Coxiella/ OR (Q fever OR coxiella OR Q-fever OR rickettsia burnetii OR rickettsia burnetii infection OR rickettsia burnetti OR rickettsiosis infection OR rickettsiosis rickettsia OR australian Q fever).ab. OR (Q fever OR coxiella OR Q-fever OR rickettsia burnetii OR rickettsia burnetii infection OR rickettsia burnetti OR rickettsiosis infection OR rickettsiosis rickettsia OR australian Q fever).ti.)
	AND
Chronic disease	(exp chronic disease/ OR chronic.ab. OR chronic.ti.)
	AND
Follow-up/screening	(exp screening/ OR exp follow-up/ OR exp cost/ OR (follow-up OR follow up OR screening OR screen* OR identif* OR reexaminat* OR long-term OR long term OR review OR strateg* OR check* OR general population OR population-based OR population based OR cost* OR cost effect* OR cost-effect*).ab. OR (follow-up OR follow up OR screening OR screen* OR identif* OR reexaminat* OR long-term OR long term OR review OR strateg* OR check* OR general population OR population-based OR population based OR cost* OR cost effect* OR cost-effect*).ti.)
	NOT
Case reports	(case study OR case studies OR case report*).ab. OR (case study OR case studies OR case report*).ti.

Selected were all articles that could provide information on the previously defined topics: serological follow-up of known acute Q-fever patients, testing known acute Q-fever patients with echocardiography for valvular lesions, detection of asymptomatic or unknown *C. burnetii* infections (screening of patients at high risk for chronic Q-fever by serological testing [i.e., patients with known valvular disease, aneurysms, vascular grafts, immunocompromised patients, and pregnant women] or conducting a general population study in an outbreak area). Articles were included for full-text assessment when selected by one of the investigators, when considered uncertain to have relevant information, or when there was no abstract available with a title suggesting relevance.

In selection step 2, full-text articles were checked for relevant information, and CocanCPG (Coordination of Cancer Clinical Practice Guidelines) checklists [22] were used to assess the quality (CW and WvdH). These checklists are designed for cancer research, but are also applicable to other research areas. However, for cross-sectional studies and case series, no checklists are available. Therefore, relevant criteria for these types of studies were determined, that is, addressing an appropriate and clearly focused question, representative population, survey method or data collection described, outcome measures defined and clearly described, response rate reported, and results relevant for the objectives of this review. The quality of guidelines was assessed with the AGREE II instrument [23], a validated instrument developed for this purpose. The reference lists of selected articles were checked for additional relevant publications that were missed by searching in PubMed and Embase. During full-text appraisal, we excluded reviews that were not systematic and did not present relevant data, studies that did not present original or relevant data, and case reports with less than five patients, as case reports were still present among the search results despite the exclusion with search terms. Selected conference abstracts without a full-text article, were also excluded, as were articles that could not be retrieved from three different libraries. Finally, the Newcastle Ottawa Scale (NOS), as recommended by the Cochrane Non-Randomized Studies Methods Working Group, was used to assess and report the quality of the included studies [24].

Data extraction

Two investigators (CW and WvdH) extracted data from the included papers and summarised relevant data in a table (S.Table 1), which included: country, start study period and duration, epidemiological situation (outbreak/endemic), and study type; total number of *C. burnetii* infections and sampling procedure; number of patients/population, development of chronic Q-fever or high IgG phase I titres, and co-morbidities or pre-existing disease; conclusion/recommendation by authors of the article; and additional comments/interpretation by the authors of this review. For screening studies, we also summarised the categories of high-risk patients included and the total number of patients screened.

Case definitions and origin of cases (inclusion data)

To place the different studies in the appropriate context, we made a distinction between studies executed during an outbreak or in an endemic situation. The variation of case definitions of acute, past-resolved, and chronic Q-fever is large, as is the definition of high titres. Therefore, inclusion criteria and definitions of cases or populations are summarised in S.Table 2.

RESULTS

Inclusion of articles

The online database search was performed on 3 August 2012, and updated with the most recent publications on 17 October 2012. The search yielded 394 articles, of which 259 were unique (Figure 1). During abstract assessment, 183 articles were excluded. Seventy-six articles were identified as potentially relevant, and were screened full-text. In the reference lists of these articles, we identified another twelve references as possibly relevant. Additionally, one not yet cited article that did not show up in the search strategy was added to the full-text assessment step [25]. Five full-text articles (two French, two Japanese, and one Ukrainian) could not be retrieved from three different libraries. Overall, 84 full-text articles were screened, and 64 were excluded because of different criteria as detailed in Figure 1. The remaining twenty articles, including one guideline, met the inclusion criteria and were included in this systematic review (fourteen found in PubMed, two in Embase, three from checking reference lists, and the one additionally added article). Fourteen articles only provided information on the follow-up of known acute Q-fever cases, four presented data on the identification of previously unknown *C. burnetii* infections, and two full-texts provided information on both topics. The sixteen articles with information on follow-up of known acute Q-fever cases contained nine outbreak-related articles, and seven studies performed in an endemic situation, of which four were descriptions of (reference) laboratory cohorts. The six articles that described detection of asymptomatic infections consisted of five outbreak-related articles and one study in an endemic area. No cost-effectiveness study was found.

Inclusion of cases

All nine studies with follow-up of known acute Q-fever cases performed during an epidemic had well defined inclusion criteria [8, 13, 15, 16, 25–29]. For studies of endemic cases and articles describing a (reference) laboratory cohort, the inclusion of cases was well defined in four studies [12, 14, 30, 31], while in three studies it was unclear where cases were derived from [7, 32, 33]. All sixteen studies with follow-up of known acute cases, independent of the epidemiological setting, included serology in their inclusion criteria [7, 8, 12–16, 25–33], while clinical characteristics were mentioned in ten studies only [7, 13, 25–27, 29–33].

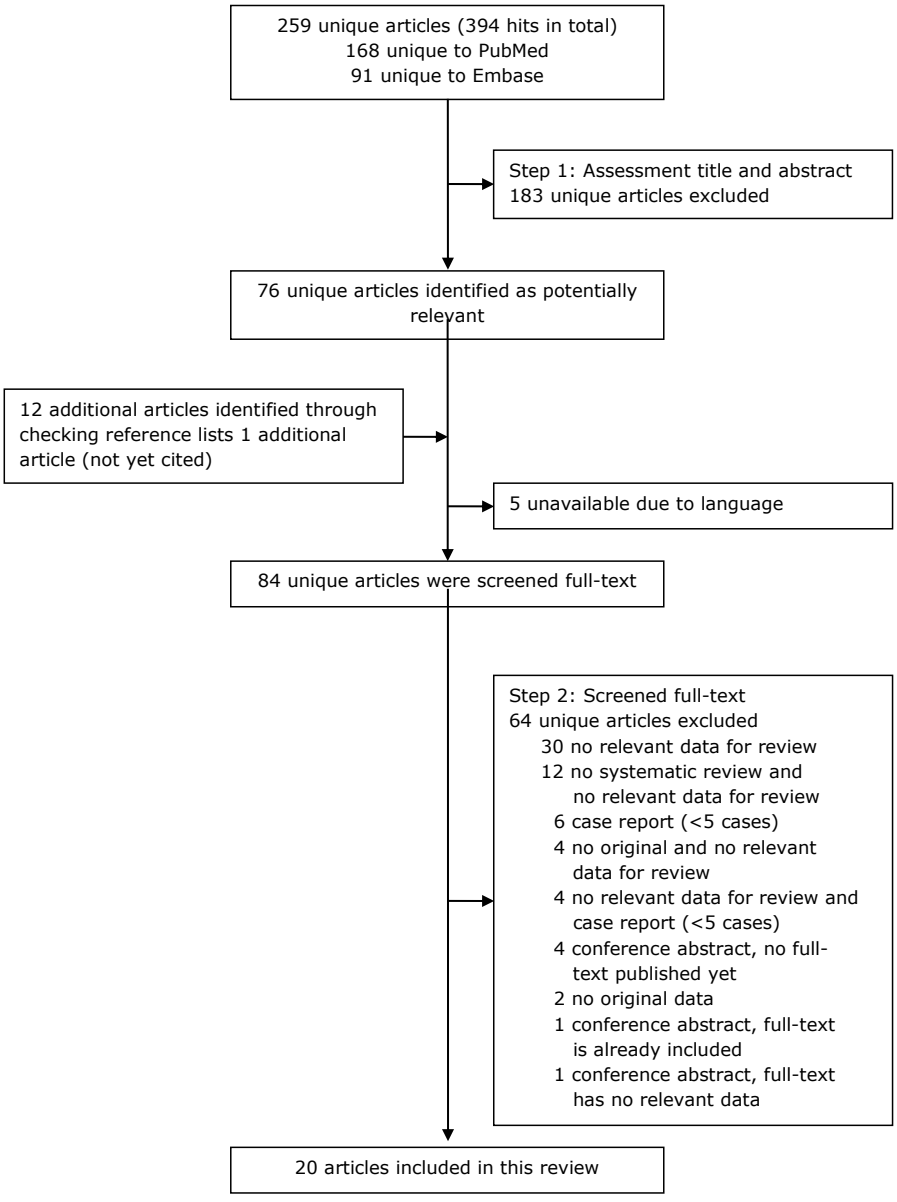

Figure 1. Flowchart of identified articles.

Chronic Q-fever was mostly well defined; fourteen studies based their definition on serology in combination with clinical characteristics [7, 10, 12, 13, 15, 20, 21, 25–27, 29–32]; five studies only used serology, clinical data or cause of death as case definition [8, 14, 16, 28, 33]; one study did not describe the development of chronic Q-fever as outcome [19].

Quality of studies included

The NOS scores are presented in S.Table 1. Most studies only performed follow-up in acute Q-fever patients without comparison with an asymptomatic or seronegative control group, and the 'comparison items' in the NOS cannot be scored in this situation. For screening studies, three of the nine possible NOS stars could not be retrieved, as these items were not applicable for these studies (e.g., outcome of interest at start study, follow-up long enough, and adequacy of follow-up). Most studies had a fair quality; however, losses to follow-up were sometimes large or not reported, endocarditis was not always confirmed to be *C. burnetii*-related, and reported numbers of cases within the same report were sometimes inconsistent (S.Table 1).

Follow-up of known acute Q-fever patients

Individual serological follow-up

Fourteen articles described or advised serological follow-up of known acute Q-fever patients [7, 8, 12–16, 25, 27, 29–33] (Table 2/S.Table 1). Four studies showed serological follow-up results, but gave no recommendation regarding serological follow-up [25, 27, 29, 33]. Serological follow-up of each acute Q-fever patient was advised by three studies, but no recommendations regarding timing and duration of follow-up were given [8, 13, 14]. Two studies only advised on patients with risk factors, recommending they should be followed "carefully" [32] or should be followed for at least two years [30]. Landais *et al.* [7] proposed to test all acute Q-fever patients systematically at three and six months after the onset of disease. Serological screening should be stopped when there is no serologic evidence for a chronic infection six months after the acute infection (IgG phase I <1:800), but further clinical assessment is needed when IgG phase I ≥1:800 [7]. Wagner-Wiening *et al.* [16] advised to test acute Q-fever patients at three, six, and twelve months after diagnosis. Hartzell *et al.* [31] recommended serological and clinical follow-up at 6, 12, 18, and 24 months, or even longer when thought to be necessary (IgG phase I titre still ≥1:1,024 at 24 months, and equivalent to or greater than the IgG phase II titre, also testing at 36 months and case-by-case assessment). Van der Hoek *et al.* [15] recommended a single follow-up at nine months for patients without risk factors (testing at three months is not useful in these patients), and a stringent follow-up scheme for patients with risk factors (i.e., at three-, six-, and twelve-month follow-up). Hung *et al*. [12] noticed that some patients without risk factors had increased IgG phase I

antibodies (≥1:800) whilst symptoms were absent and concluded that continued serological follow-up in these patients is not needed.

Echocardiography

Six studies investigated or made recommendations for targeted case finding of heart valve lesions with echocardiography in acute Q-fever patients [7, 8, 12, 13, 26, 31]. Limonard *et al.* performed a baseline transthoracic echocardiography (TTE) in 66/85 (78%) of his patients (standard care in the Netherlands at that time), and concluded that echocardiography of every acute Q-fever patient is not useful, since 39/66 (59%) patients showed evidence for valvulopathy using TTE, while none developed chronic Q-fever [13]. Ayres *et al.* also found no evidence for differences in echocardiography abnormalities after 10-year follow-up between acute Q-fever cases and controls [26]. Hartzell *et al*. advised to use echocardiography only for acute Q-fever patients with an indication (known valvulopathy, cardiac symptoms or a significant cardiac murmur on physical examination), as they also found trivial valvulopathies in at least 60% in military personnel with Q-fever [31]. Two studies recommended TTE in all acute Q-fever patients in order to detect minimal valvular diseases [7, 8], based on results from a case report by Fenollar *et al*. [18]. Landais *et al.* also recommended to perform a transoesophageal echocardiogram (TEE) in patients with IgG phase I ≥1:800 [7]. Hung *et al.* gave patients the possibility for a TEE, but all participants who accepted medical consultation declined to be screened (n=4), though none developed chronic Q-fever [12].

Risk of chronic infection and time from acute to chronic Q-fever

The risk to evolve from acute to chronic Q-fever, with endocarditis as the main clinical presentation, or to develop high IgG phase I titres, was described in fourteen studies [7, 8, 12, 13, 15, 16, 25–30, 32, 33] (Table 2/S.Table 1). The conversion rate of acute to chronic Q-fever ranged from 0.0% to 5.0%, with follow-up ranging from two months to twelve years [8, 12, 13, 15, 25–30, 32, 33]. High IgG phase I titres ranged from 0% at six years to 50% at three months following acute Q-fever [13–16, 25]. The time to progress from acute to chronic Q-fever was investigated in four studies [7, 8, 30, 32]. Fenollar *et al.,* reported a median time of 6 months (range 1–18 months) [30], and Landais *et al.* found a median time of 3 months (range 1–48 months) with progression within 6 months in 77% of the acute cases [7]. Raoult *et al.* reported a range of six months to three years [32], and Tissot-Dupont *et al.* observed all chronic cases within one year after acute Q-fever [8]. Overall, time to develop chronic Q-fever after an acute infection ranged from one month to four years, though the majority of chronic cases were observed within six months. Between 32% to 100% of chronic Q-fever cases had pre-existing valvular disease, and 16% to 96% had pre-existing vascular disease according to studies from the database of a large reference centre [7, 30, 32]. In the only outbreak study

Table 2. Overview of the 20 included studies describing (a) follow-up of known acute Q-fever patients and (b) detection of asymptomatic or unknown *C. burnetii* infections. The studies are categorised in chronological order of start study for both topics.

(a) Follow-up of known acute Q-fever patients

Ref.	Country; start study period	Epidemiologic situation	Follow-up/ data collection duration	Total no. CBI[a]	No. with FU	Developed chronic Q-fever/ endocarditis or high IgGI[b]	Recommendation	
							Serological FU	Other
Reilly [14]	UK; 1972	Endemic	0–14yr FU	103	23/46 (50.0%) ≥1yr FU	CQ: NR; IgGI >1:512: 1/46 (2.2%)	All QF prolonged FU, details NR	Also clinical FU
Soriano [33]	Spain; 1983	Endemic	2–88mo FU	20	10 AQ, 10 CQ	CQ: 0/10 (0%)	No recommendation	NA
Lovey [28]	Switzerland; 1983	Outbreak	12yr FU	797	411 AQ (40 died), 386 PQ (55 died), 1247 controls (87 died)	EC: 3/411 AQ (0.7%), 9/1247 controls (0.7%)	No recommendation (no serology done)	NA
Raoult [32]	France; 1985	Endemic	13yr DC	1383	NR	CQ: 16/1086 (1.5%); CQ with AQ history: 19/313 (6.1%)	QF with host factors (pregnant women, vascular/valvular lesion, cirrhosis or cancer): follow "carefully"	NA
Fenollar [30]	France; 1985	Endemic	15yr DC	1666	NR	CQ EC: R: 12/1569 (0.8%), P: 7/97 (7.2%)	AQ with clinical history of valvulopathy FU ≥2yrs every 3mo; improving FU necessary	All AQ: screen for clinical history of valvulopathy
Landais [7]	France; 1985	Endemic	NR	NR	NR	CQ EC: 22 (denominator NR)	All AQ FU at 3 and 6mo; PCR and FU if IgGI ≥1:800 at 6mo	All AQ TTE; TEE if IgGI ≥1:800 at 6mo
Ayres [26][c]	UK; 1989	Outbreak	10yr FU	147	85 with complete FU	CQ EC: 2/147 (1.4%)	No recommendation (serology performed at 12yr FU in 92/147 cases [29])	NA

(a) Follow-up of known acute Q-fever patients (continued)

Ref.	Country; start study period	Epidemiologic situation	Follow-up/ data collection duration	Total no. CBI[a]	No. with FU	Developed chronic Q-fever/ endocarditis or high IgGI[b]	Recommendation	
							Serological FU	Other
Marmion [29][c]	UK; 1989	Outbreak	12yr FU	147	92	CQ EC (probable): 1/92 (1.1%)	No recommendation	NA
Kováčová [27]	Slovakia; 1993	Outbreak	10–30–50mo FU	113	10mo: 103, 30mo: 40, 50mo: 27	CQ: 0/113 (0.0%)	No recommendation	NA
Hussain-Yusuf [25]	UK; 2002	Outbreak	6yr FU	129	38	CQ EC: 1/38 (2.6%); IgGI ≥1:800: 0/38 (0%)	No recommendation	NA
Tissot-Dupont [8]	France; 2002	Outbreak	FU NR, 1 yr inclusion	101d	NR(578 without FR,489 with FR screened)	CQ:5/101 (5.0%),1 pregnant women, 1 cardiovascular (2/16 with RF), 3/85 without RF	All AQ after outbreak systematic FU	All AQ:detect minimal valvular disease;screen:any person at risk and all pregnant women (outbreak),febrile pregnant women or after abnormal delivery(endemic)
Wagner-Wiening [16][e]	Germany; 2003	Outbreak	8–60wk FU	177	30/171 AQ (263 screened, 92 no antibodies), with RF NR (6 AQ, 29 screened, 23 no antibodies)	IgGI >1:512/treated as CQ: 3/30 (10.0%); CQ with RF: 1/4 (25.0%) pregnant women, 0/2 (0.0%) valvular patients	All AQ FU at 3, 6, and 9mo	Screen pregnant women and valvular patients in outbreak independently of symptoms
Hung [12]	Taiwan; C1: 2004,C2: 2009	Endemic	C1: 5–43mo; C2: 5–8mo FU	311	C1: 92/273 FU, C2: 28/38 FU	CQ: 0/120 (0.0%); IgGI ≥1:800: C1: 17/92 (18.5%), C2: 1/28 (3.6%)	Asymptomatic after AQ with high IgGI without RF no continued FU	NA

(a) Follow-up of known acute Q-fever patients (continued)

Ref.	Country; start study period	Epidemiologic situation	Follow-up/ data collection duration	Total no. CBI[a]	No. with FU	Developed chronic Q-fever/ endocarditis or high IgGI[b]	Recommendation	
							Serological FU	Other
Limonard[13]	the Netherlands; 2007	Outbreak	1yr (FU 3–6–12mo)	85	3mo: 42, 6mo: 69, 12mo: 64 (all 85 had clinical FU at 3–6mo, 84 at 12mo as 1 patient died, unrelated to QF)	CQ: 0/85 (0.0%); IgGI ≥1:800: 3mo 21 (50.0%), 6mo 13 (18.8%), 12mo 2 (3.1%)	All AQ FU is advisable, details NR	Also clinical FU; TTE for all AQ not useful
van der Hoek [15]	the Netherlands; 2007	Outbreak	1yr (FU 3–6–12mo)	686	3mo: 622, 6mo: 587, 12mo: 686	CQ: 11/686 (1.6%); IgGI ≥1:1,024: 3mo 84 (14.3%), 6mo 46 (8%), 12mo 32 (4.6%)	AQ with RF stringent FU, without RF FU at 9mo	AQ without RF 3mo FU not useful
Hartzell [31]	USA; NR	Endemic (military personnel)	5yr DC	>150	NR	NR	All AQ every 6mo for 2yrs	Also clinical FU; echocardiography only on indication (valvulopathy/ cardiac murmur)

(b) Detection of asymptomatic or unknown C. burnetii infections

Ref.	Country; start study period	Epidemiologic situation	High-risk patients	Duration of inclusion/data collection	Total no. screened	No. past-resolved Q-fever, chronic Q-fever, seropositive[b]	Recommendation
Fournier [10]	France; 1995	Endemic	Aneurysm, vascular graft surgery	2yr	163	2 CQ, no. seropositive NR	Patients with aneurysm or vascular graft with unexplained fever, abdominal pain, or weight loss: systematic *CB*-testing
Kampschreur [19]	the Netherlands; vascular 2009, valvular 2010	Outbreak	Aortic aneurysm, central vascular reconstruction, cardiac valve surgery history	With history and 1.5yr prospectively (valvular only)	785	84 seropositive (10.7%): vascular 31/276 (11.2%), valvular 53/509 (10.4%)	Clinicians in high-incidence QF regions should be alert for CQ in high-risk patients, even if no AQ episode is reported
Kampschreur [20]	the Netherlands; 2010	Outbreak	Cardiac valve surgery history	With history	568	116 PQ or CQ (4 proven CQ, 5 probable CQ)	Patients with history of valve surgery: screen *CB* antibodies in outbreak
Wegdam-Blans [21]	the Netherlands; 2010	Outbreak	Known aortic aneurysm, heart valve/vascular/ endovascular prosthesis	With history from 2000 on and 1yr prospectively	763	42 PQ, 10 CQ	Targeted screening programme is advisable

AQ: acute Q-fever; C1: cohort 1; C2: cohort 2; *CB*: *Coxiella burnetii*; CBI: *Coxiella burnetii* infection; CQ: chronic Q-fever; DC: data collection; EC: endocarditis; FU: follow-up; IgGI: anti-phase IgG I titre; IgGII: anti-phase IgG II titre; mo: month; no.: number; NA: not applicable; NR: not reported; PCR: polymerase chain reaction; pos: positive; PQ: past-resolved Q-fever; QF: Q-fever; P: prospective study; R: retrospective study; RF: risk factors; TEE: transoesophageal echocardiogram; TTE: transthoracic echocardiogram; wk: week; yr: year.

[a] Total number of *C. burnetii* infections in the original outbreak or total number of *C. burnetii* infections described in an endemic situation.

[b] For case definitions, see S.Table 2.

[c] Data focusing on Q-fever fatigue syndrome (QFS) are not included in this systematic review.

[d] Fifty-nine patients with residual antibodies not included.

[e] Includes follow-up of known acute Q-fever cases and screening of high-risk groups in order to detect asymptomatic or unknown *C. burnetii* infections.

that investigated pre-existing cardiovascular diseases in chronic Q-fever patients, 36% had pre-existing valvular disease and 18% had pre-existing vascular disease [15].

Detection of asymptomatic or unknown *C. burnetii* infections

Targeted screening in high-risk patients

Six studies performed targeted screening for high-risk patients [8, 10, 16, 19–21] (Table 2/S. Table 1). One study focused on vascular patients (aneurysm or vascular graft) [10], another study only included patients with heart valve disease [20], two studies performed screening for vascular as well as valvular patients [19, 21]. The fifth study included pregnant women, cardiovascular patients, and persons with immunodeficiencies [8], while the last study screened pregnant women and valvular patients [16].

The five studies that were conducted because of a Q-fever outbreak detected *C. burnetii* antibodies in 7% to 21% of screened patients [8, 16, 19–21], and all advised screening of those at risk for chronic infection during outbreaks.

Two studies recommended testing of all pregnant women in outbreak situations, regardless of symptoms [8, 16]. In an endemic situation, however, Tissot-Dupont *et al.* stated that testing of pregnant women is only necessary when women are febrile or had an abnormal delivery [8].

Valvular damage or vegetations confirmed by echocardiography among chronic Q-fever cases as presented in two studies ranged from 0% to 11% [20, 21]. Among the screened population, the detection rate of chronic Q-fever infections ranged from 0.4% to 3.4% [8, 10, 16, 20, 21], with a rate of 1.2% in the only study performed in an endemic area [10]. No additional chronic Q-fever cases were observed at three and six months after initial screening in Kampschreur *et al.* [20].

General population study

Although two studies screened people without known risk factors or visitors of the source of infection [8, 16], we found no reports on general population surveys in outbreak areas. One of these studies performed active serological surveillance after an outbreak, though sampling was not performed systematically but on the people's own initiative [8].

DISCUSSION

The majority of studies investigating serological follow-up of acute Q-fever patients conclude that follow-up is needed, but recommendations about optimal timing, frequency, and duration were inconsistent. Recent studies promote a more stringent follow-up for patients with risk factors than for patients without risk factors [7, 12, 15, 31]. Problems encountered in various studies are the identification of proven chronic infections, the distinction between possible, probable, and proven infections [34], the unknown incubation period, the non-specific clinical diagnosis and non-sensitive laboratory diagnosis. All these factors may contribute to prolonged follow-up or start of treatment of patients with titres indicative for chronic Q-fever but without symptoms or risk factors for chronic disease. Hung *et al.* found that high IgG phase I antibody titres eventually resolved and suggested that continued serological follow-up in asymptomatic patients with high IgG phase I titres and no predisposing factors might not be necessary [12]. As most chronic Q-fever cases are diagnosed within the first year after acute Q-fever [7, 8, 30, 32], it might well be that late cases are due to delayed diagnosis, as a result of not recognising the disease rather than a long incubation time.

Three studies that recommended echocardiography for all acute Q-fever patients were not included in this systematic review, as one study only presented three cases [18], and two did not present original data [2, 17]. Two of the included studies [7, 8] adapted the advice of Fenollar *et al.* to screen all acute Q-fever patients with echocardiography [18]. Data from the Netherlands, Taiwan, UK, and USA do not support the screening of all acute Q-fever cases for heart valve damage by echocardiography in addition to serological follow-up, because this would probably cause over diagnosis of valvulopathies that are not predictive for the development of chronic Q-fever [12, 13, 20, 21, 26, 30, 31].

Studies investigating targeted screening strategies for high-risk patients recommended screening in outbreak settings [8, 16, 19–21]. However, the implementation of a screening programme depends on the extent of an outbreak, and standard criteria should be applied to assess whether screening is indicated [35]. Screening of pregnant women is a matter of debate as well. Some studies recommend screening of all pregnant women in an outbreak situation [8, 16], as it is reported that they have an increased risk for chronic Q-fever and adverse pregnancy outcome [36], while other studies did not find a higher risk for adverse pregnancy outcome and do therefore not recommend to screen all pregnant women [37, 38].

Most of the studies included in this review had a fair quality, although the inclusion of cases was not always well defined, losses to follow-up were sometimes large, endocarditis was not always confirmed to be *C. burnetii*-related, and inconsistencies in reporting were noticed.

Different case definitions for chronic Q-fever and the use of different serological tests and cut-off values make comparison of studies difficult (S.Table 2). The case definition of chronic

Q-fever is still a matter of debate [34, 39, 40]. A Dutch consensus group classified chronic Q-fever cases as proven, probable, or possible [34]. Proven chronic Q-fever cases have a positive *C. burnetii* PCR (or culture) in blood or tissue (in the absence of acute infection), or a high phase I IgG titre (≥1:800 for in-house developed IFA and ≥1:1,024 for commercial IFA) in combination with confirmed endocarditis according to the revised Duke criteria [41], or evident infection of aneurysm or vascular graft on computed tomography (CT), fluorodeoxyglucose positron emission tomography combined with CT (FDG-PET-CT), duplex ultrasound or magnetic resonance imaging (MRI). Probable chronic *Q-fever* patients have an IgG phase I ≥1:1,024 with risk factors for chronic Q-fever and echocardiographic abnormalities that do not meet the revised Duke criteria [41]. Rare manifestations of chronic Q-fever (e.g., hepatitis, osteomyelitis) or signs of systemic inflammation might be present. Possible chronic Q-fever cases have an IgG phase I ≥1:1,024, without any of the manifestations mentioned in the categories proven and probable. For each category, specific recommendations for follow-up and treatment of patients are presented [34]. Another issue is that chronic Q-fever is relatively rare, and small sample sizes hamper the assessment of the best follow-up strategy and risk for a chronic infection.

The rates of developing chronic Q-fever between countries ranged from 0% to 5.0% [8, 12, 13, 15, 25–30, 32, 33]. The risk to develop chronic Q-fever, however, might be overestimated in studies with a high percentage of people with pre-existing valvular or vascular disease. Such high rates of pre-existing cardiovascular diseases are unlikely to be representative for populations from which average acute Q-fever patients originate.

Further, we made a distinction between studies that were performed in an outbreak or in an endemic situation. This might be relevant since the acute disease might be easier to detect in an outbreak situation, as the timing of infection can be estimated more precisely, compared to an endemic situation or information obtained from a (reference) laboratory database.

Remarkable is the fact that in some countries, Taiwan and Slovakia for example, no chronic Q-fever cases have been diagnosed so far, despite acute Q-fever outbreaks [12, 27], in contrast to France, UK, Germany, and the Netherlands [7, 8, 10, 15, 16, 19–21, 26, 29, 30, 32, 42].

Three articles included in the present review are frequently cited and provide information from the large database of the French National Reference Centre [7, 30, 32]. However, study periods of the different reports showed overlap and for the chronic Q-fever cases it was not always clear whether they had been included in one or more studies.

In conclusion, selective serological follow-up for acute Q-fever patients with risk factors for chronic Q-fever infection is highly recommended, although there is no consensus on the frequency, timing, and duration. For acute Q-fever patients without known risk factors, follow-up is recommended at least once, but should be performed later than three months

after the acute Q-fever infection, for example at six or nine months. Echocardiography should be reserved for acute Q-fever patients with a clinical indication of cardiac abnormalities. In an outbreak setting, screening of all patients with heart valve disease, vascular prosthesis or aneurysm might be useful. In general, data on cost-effectiveness are lacking, although screening of pregnant women was not cost-effective in a study performed in the Netherlands [43]. The implementation of screening strategies is highly dependent on the extent of the outbreak. We found no evidence that a general population study in an outbreak area would be useful. Major issues to be resolved are the definition of acute cases, the risk for chronic Q-fever in asymptomatic cases, the incubation period of chronic Q-fever, and finally the true incidence of chronic Q-fever. These issues can only be addressed with long-term follow-up studies that are difficult, if not impossible to implement in the absence of a large Q-fever epidemic.

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APPENDIX SUPPLEMENTARY INFORMATION

Table 1. More detailed summary of the 20 included studies describing (a) follow-up of known acute Q fever patients and (b) detection of asymptomatic or unknown *C. burnetii* infections. The studies are categorised in chronological order of start study for both topics.

(a) Follow-up of known acute Q fever patients

Ref.	Country; start study period, duration; epidemiologic situation; study type	Total no. CBI[a]; sampling procedure follow-up	No. of patients or population[b] / developed chronic Q fever or high IgGI[b] / co-morbidities / pre-existing disease	Conclusion / recommendation	Comments / interpretation	NOS score[c] S	C	O
Reilly [14]	UK; 1972, 0−14yr FU; endemic; RCS	n=103; non-systematic CFT	AQ: n=46, PQ: n=10, CQ: n=5; AQ to CQ: NR; 50% had FU for ≥1yr; high IgGI ≥1:192: 3/46 (4.7%), IgGI >1:512: 1/46 (2.2%)	All QF cases prolonged serological and clinical FU, details NR	FU no. and outcome not clear; old data but FU up to 14yr	★★★☆	☆☆	★★
Soriano [33]	Spain; 1983, 2−88mo FU, mean 35.8mo; endemic; RCS	n=20; non-systematic CFT and IFA	AQ: n=10, CQ: n=10; EC serological profile (IgA≥1:640): 0 (0%) AQ, though 2 had IgGI ≥1:1,280	No FU recommendation; no AQ showed serological profile for EC	Small n; outcomes not clear; 2 AQ had high IgGI, possible CQ NR; only healthy AQ included in FU, selection bias?	★☆	☆☆	★★
Lovey [28]	Switzerland; 1983, 12yr FU; outbreak; PC/FUS	n=797; no serology in FU	AQ: n=411, PQ: n=386, controls: n=1,247; AQ to CQ EC: 3 AQ (0.7%), 9 controls (0.7%), RR 1.0, 95% CI 0.9−1.1; deceased: 40 AQ (9.7%), 87 control (7.0%)	No FU recommendation (no serology done); no difference in incidence of EC between AQ and controls; risk of arterial disease significantly higher among AQ (6.8%) vs control (3.8%)	Long FU; no serological FU: no confirmation of relation EC to CBI; CQ missed as post mortem examinations only performed in ~20%?	★★★★	★	★
Raoult [32]	France; 1985, 13yr DC; endemic RCS	n=1,383; non-systematic in-house IFA	AQ: n=1,070, CQ: n=313 (included 229 EC (194 reported) and 25 vascular infection)); AQ to CQ: 16/1,086 (1.5%); CQ with AQ history: 19/313 (6.1%), 6 (31.6%) pre-existing valvular disease, 3 (15.8%) abdominal AA, 6 (31.6%) pregnant women, 4 (21.1%) other; CQ EC: pre-existing valvular disease 172/194 (88.6%); vascular infection CQ: 24/25 (96.0%) pre-existing vascular abnormality	Follow patients with host factors (pregnancy, vascular/valvular lesion, cirrhosis or cancer) “carefully”	Unclear whether CQ were also included in [30] and/or [7]; data are inconsistent; denominator FU NR	★★☆	☆☆	★
Fenollar [30]	France; 1985, 15yr DC; endemic; RCS, PC/FUS	n=1,666; non-systematic in-house IFA	AQ (R): n=1,569; AQ to CQ EC: 12 (0.8%), 12 (100.0%) pre-existing valvular disease; AQ (P): n=97; AQ to EC: 7 (7.2%), 21 (21.6%) valvulopathy	All AQ: screening for clinical history of valvulopathy (if so: treatment and FU ≥2yrs every 3mo); improving FU necessary	Unclear whether CQ were also included in [32] and/or [7]; study period and data inconsistent and NR for P	★★☆	☆☆	★
Landais [7]	France; 1985, duration NR; endemic; RCS	n=NR; non-systematic in-house IFA	AQ: NR; AQ to CQ EC: 22; FU NR; pre-existing and known cardiovascular abnormalities 17 (77.2%)	All AQ serological FU at 3 and 6mo and TTE; if IgGI ≥1:800 at 6mo: PCR, TEE, FU	Unclear whether CQ were also included in [32] and/or [30]; end of study period and denominator NR	★★☆	☆☆	★
Ayres [26][d]	UK; 1989, 10yr FU; outbreak; PC/FUS	n=147; no serology in 10yr FU	AQ: n=147 (FU n=85 with complete FU); AQ to CQ EC: 2/147 (1.4%); co-morbidities 25/85 (29.4%) cases vs. 22/75 (29.3%) controls with FU	No FU recommendation (serology performed at 12yr FU in 92/147 cases [29]); chronic heart disease following AQ is rare and limited to EC	Focus mainly on QFS; CQ EC not confirmed; unclear whether the 92 cases with 12yr serological FU [29] included all 85 cases with FU; high incidence of co-morbidity	★★★★	★★	★★★

Ref.	Country; start study period, duration; epidemiologic situation; study type	Total no. CBI[a]; sampling procedure follow-up	No. of patients or population[b] / developed chronic Q fever or high IgGI[b] / co-morbidities / pre-existing disease	Conclusion / recommendation	Comments / interpretation	NOS score[c]		
						S	C	O
Marmion [29][d]	UK; 1989, 12yr FU; outbreak; PC/FUS	n=147; non-systematic IFA and CFT	AQ: n=147 (FU n=92); AQ to CQ EC (probable): 1 (1.1%)	No FU recommendation	Data from Australia QFS cohort not included; cohort is also described in [26]	★★★☆	☆☆	★★
Kováčová [27]	Slovakia; 1993, 10−50mo FU; outbreak; PC/FUS	n=113; systematic range of serology at 10−30−50mo	AQ: n=113 (10mo FU: n=103, 30mo FU: n=40, 50mo FU: n=27); AQ to CQ: 0 (0.0%)	No FU recommendation	Never CQ diagnosed in Slovakia so far (clinically or serologically) despite AQ outbreaks; large decrease in FU rates	★★★★	☆☆	★★
Hussain-Yusuf [25]	UK; 2002, 6yr FU; outbreak; PC/FUS	n=129; non-systematic MIF and PCR at 6yr	AQ: n=129 (FU n=38); AQ to CQ EC: 1 (2.6%); IgGI ≥1:800: 0 (0.0%)	No FU recommendation	Detection of CQ was not aim of the study	★★★★	☆☆	★★
Tissot-Dupont [8][f]	France; 2002; 1yr inclusion, FU duration NR; outbreak; PC/SHRG	n=101[e] (screened: n=1,067 (n=578 without RF, n=489 with RF); in-house IFA for different groups	AQ: n=101; AQ in 85/578 (14.7%) without known RF, 11/379 (2.6%) pregnancies (376 pregnant women), 5/91 (5.5%) cardiovascular patients, 0/19 (0.0%) immunodeficient patients; AQ to CQ: 5/101 (5.0%), 1 pregnant women, 1 cardiovascular patient, and 3 people without known RF (all symptomatic AQ, no conclusions on CQ could be drawn in 1), CQ: 2/489 (0.4%) high-risk patients	All AQ: after outbreak systematic serological FU, detect minimal valvular disease; epidemic: test any person considered to be at risk (once) and all pregnant women; endemic: test febrile pregnant women or after abnormal delivery	Important study, first time that active serologic surveillance was performed, no recommendations on timing of FU	★★★★	☆☆	★
Wagner-Wiening [16][f]	Germany; 2003, 8−60wk FU; outbreak; PC/SHRG	n=177 (screened: n=292 (n=263 exposed, n=29 high-risk); ELISA for different groups	AQ: n=171 (FU n=30); high IgGI >1:512/treated as CQ: 3 (10.0%); high-risk AQ: 4/11 (36.4%) pregnant women, 2/18 (11.1%) valvular patients, overall 6/29 (20.7%); AQ to CQ: 1 (25.0%) pregnant women, and 0 (0.0%) valvular patients, 3.4% of screened population	All AQ serological FU at 3, 6, and 9mo; screen pregnant women and people with valvular defects in outbreak situation, independently of developing symptoms	No description of clinical findings in CQ; not clear how conclusion is based on data presented (FU intervals NR)	★★★☆	☆☆	★
Hung [12]	Taiwan; C1: 2004, 5−43mo FU; C2: 2009, 5−8mo FU; endemic; PC/FUS	n=311; non-systematic IFA	AQ C1: n=273 (FU n=92), AQ C2: n=38 (FU n=28); AQ to CQ: 0/120 (0.0%); IgGI ≥1:800: C1: 17 (18.5%), C2: 1 (3.6%)	Asymptomatic after AQ with high IgGI without RF no continued serological FU	So far no CQ described in Taiwan despite occurrence of AQ	★★★☆	☆☆	★★
Limonard [13]	the Netherlands; 2007, 1yr FU; outbreak; PC/FUS	n=85; systematic IFA and CFT at 3−6−12mo	AQ: n=85; AQ to CQ: 0 (0.0%); IgGI ≥1:800: baseline 7/58 (12.1%), 3mo 21/42 (50.0%), 6mo 13/69 (18.8%), 12mo 2/64 (3.1%), all 85 had clinical FU at 3−6mo, 84 at 12mo (1 patient died, unrelated to QF); co-morbidities 26 (30.6%), 4 (4.7%) pre-existing valvular disease, 1 (1.1%) pre-existing vascular disease, 1 (1.1%) immunosuppressive therapy	All AQ serological and clinical FU is advisable, details NR; TTE of each AQ not useful	Baseline screening TTE no longer part of standard work-up of AQ in the Netherlands	★★★☆	☆☆	★★★

Ref.	Country; start study period, duration; epidemiologic situation; study type	Total no. CBI[a]; sampling procedure follow-up	No. of patients or population[b] / developed chronic Q fever or high IgGI[b] / co-morbidities / pre-existing disease	Conclusion / recommendation	Comments / interpretation	NOS score[c] S	C	O
van der Hoek [15]	the Netherlands; 2007, 1yr FU; outbreak; PC/ FUS	n=686; systematic IFA at 3−6−12mo	AQ: n=686; AQ to CQ: 11 (1.6%), FU max 3.5yr; IgGI ≥1:1,024: 3mo 84 (13.5%), 6mo 46 (7.8%), 12mo 32 (4.7%), asymptomatic 35 (5.1%); 4 (36.4%) pre-existing valvular disease, 2 (18.2%) pre-existing vascular disease, 5 (45.5%) no/ unknown	AQ with RF stringent FU, without RF FU at 9mo (3mo FU not useful); essential to distinguish AQ with RF and without	Large no. of patients with FU; additional CQ cases might become apparent	★★★☆	☆☆	★★★
Hartzell [31]	USA; 5yr DC; endemic/ surveillance; guideline	n>150; guideline for USA military personnel	AQ: n>150 USA military personnel since 2007	All AQ serological and clinical FU every 6mo for 2 yrs; echocardiography only on indication (AQ with valvulopathy or cardiac murmur)	Included as guideline and only study from US	NA	NA	NA

(b) Detection of asymptomatic or unknown C. burnetii infections

Ref.	Country; start study period, duration; epidemiologic situation; study type	High-risk patients	Total no. screened; sampling procedure	No. of patients[b], population, seropositive / pre-existing disease	Conclusion / recommendation	Comments / interpretation	NOS score[c] S	C	O
Fournier [10]	France; 1995, 2yr inclusion; endemic; PC/SHRG	Aneurysm, vascular graft surgery	n=163; in-house IFA, PCR vascular biopsy	*CB* serology pos: NR; *CB* isolated: 2 (1.2%), 1 AA, 1 aortic prosthesis; 129 (79.1%) AA, 24 (14.7%) iliac aneurysm, 5 (3.1%) aortic prosthesis, 5 (3.1%) popliteal aneurysm	Cases with an aneurysm or vascular graft with unexplained fever, abdominal pain, or weight loss: consider QF diagnosis, systematic serological *CB*-testing	Characteristics of the 163 screened patients NR; also includes description of 13 CQ cases with CBI of aneurysm or vascular graft	★★☆☆	☆☆	★☆☆
Kampschreur [19]	the Netherlands; vascular 2009, valvular 2010, inclusion with history (both) and 1.5yr prospectively (vascular only); outbreak; PRC/ SHRG	Aortic aneurysm, central vascular reconstruction, cardiac valve surgery history	n=785; IFA	*CB* IgGII ≥1:128 (total seropositive): 84 (10.7%, 95% CI 8.5−12.9), vascular 31/276 (11.2%, 95% CI 7.5−14.9); valvular: 53/509 (10.4%, 95% CI 7.8−13.1), cut-off ≥1:64 seropositive: 117 (14.9%)	Clinicians in high-incidence QF regions should be alert for CQ in high-risk patients, even if no AQ episode is reported	Valvular cases are also included in [20]; seroprevalence not corrected for background seroprevalence; development of CQ NR	★★☆☆	☆☆	★☆☆
Kampschreur [20]	the Netherlands; 2010, inclusion with history; outbreak; PC/SHRG	Cardiac valve surgery history	n=568; IFA, PCR if IgGI ≥1:512	CQ or PQ: n=116 (20.4%); proven/probable CQ: 9 (7.8%), 1.6% screened population, 4 (44.4%) PCR pos, asymptomatic CQ 7 (77.8%)	Patients with history of valve surgery: screening for *CB* antibodies is recommended in outbreak	Some valvular patients also presented in [19]; seroprevalence not corrected for background seroprevalence; medical records of deceased patients checked	★★☆☆	☆☆	★☆☆

Ref.	Country; start study period, duration; epidemiologic situation; study type	High-risk patients	Total no. screened; sampling procedure	No. of patients[b], population, seropositive / pre-existing disease	Conclusion / recommendation	Comments / interpretation	NOS score[c] S	C	O
Wegdam-Blans [21]	the Netherlands; 2010, inclusion from 2000 on and 1yr prospectively; outbreak; PRC/SHRG	Known aortic aneurysm, vascular/ endovascular/ heart valve prosthesis	n=763; IFA, PCR	PQ: n=42, CQ: n=10, total CB seropositive: n=52 (6.8%), CQ 1.3% of screened population: CQ: 2 (20.0%) PCR pos, asymptomatic CQ 9 (90.0%), 4 (40.0%) vascular prosthesis, 3 (30.0%) heart valve prosthesis, 3 (30.0%) combined prosthesis, no AA	A targeted screening programme is advisable	Includes hypothetical cost overview; hypothesis that CQ is continuous process that follows symptomatic AQ	★★☆☆	☆☆	★☆☆

95% CI: 95% confidence interval; AQ: acute Q fever; C1: cohort 1; C2: cohort 2; *CB*: *Coxiella burnetii*; CBI: *Coxiella burnetii* infection; CFT: complement fixation test; CQ: chronic Q fever; DC: data collection; EC: endocarditis; FU: follow-up; IFA: indirect immunofluorescence assay; IgGI: anti-phase IgG I titre; IgGII: anti-phase IgG II titre; MIF: micro-immunofluorescence; med: median; mo: month; NA: not applicable; neg: negative; no.: number; NR: not reported; PCR: polymerase chain reaction; pos: positive; PQ: past-resolved Q fever; QF: Q fever; QFS: Q fever fatigue syndrome; P: prospective study; PC/FUS: prospective cohort/follow-up study; PC/SHRG: prospective cohort/screening high-risk groups; PRC/SHRG: prospective and retrospective cohort/screening high-risk groups; R: retrospective study; RCS: retrospective case series; RF: risk factors; RR: risk ratio; TEE: transesophageal echocardiogram; TTE: transthoracic echocardiogram; vs: versus; wk: week; yr: year.

[a] Total number of *C. burnetii* infections in the original outbreak or total number of *C. burnetii* infections described in an endemic situation.

[b] For case definitions, see Table 2.A2.

[c] Newcastle-Ottawa Scale (NOS): S=selection (maximum of 4 stars), C=comparability (maximum of 2 stars), O=outcome (maximum of 3 stars); ★: star earned; ☆: item not applicable.

[d] Data focusing on Q fever fatigue syndrome (QFS) are not included in this systematic review.

[e] Fifty-nine patients with residual antibodies not included.

[f] Includes follow-up of known acute Q fever cases and screening of high-risk groups in order to detect asymptomatic or unknown *C. burnetii* infections.

Table 2. Definition of acute, past-resolved, and chronic Q fever or high titre. The studies are categorised in chronological order of start study for follow-up of known acute Q fever patients and detection of asymptomatic or unknown *C. burnetii* infections.

(a) Follow-up of known acute Q fever patients

Ref.	Country; start study period	Definition acute Q fever		Definition past-resolved Q fever		Definition chronic Q fever / high titre	
		Serology	Clinical	Serology	Clinical	Serology	Clinical
Reilly [14]	UK; 1972	≥Fourfold rise in phII titre or a stable phII ≥1:80 (CFT)	NCSI, if stable phII ≥1:80 NS	NA	NA	CQ: phI and phII >1:512 at presentation and persistence of illness for several months; HT among previous AQ: phI ≥1:192	NCSI
Soriano [33]	Spain; 1983	PhII antigen seroconversion (CFT, Virion)	NS	NA	NA	Serological tests, titre NS, and when possible isolation of the micro-organism from tissues; endocarditis serological profile: IgA ≥1:640	Endocarditis, details NR
Lovey [28]	Switzerland; 1983	≥Fourfold increase in titre between 2 serum samples or IgM ≥1:20 (CFT and IFA)	NCSI	IgGII ≥1:20 without IgM	NCSI	No serology	Endocarditis (cause of death, associated disease on death certificate, or cited as a medical problem in questionnaire)
Raoult [32]	France; 1985	IgGII ≥1:200 and IgMII ≥1:50 (in-house IFA), clinical findings considered when IgGI ≥1:800	Isolated fever, hepatitis, pulmonary or nervous system involvement, pericarditis, myocarditis	NA	NA	IgGI ≥1:800	Endocarditis, vascular infection, osteoarticular infection, chronic hepatitis, pregnancy, other
Fenollar [30]	France; 1985	IgGII ≥1:200 and IgMII ≥1:50 (in-house IFA), clinical findings considered when IgGI ≥1:800	NCSI, if IgGI ≥1:800 NS	NA	NA	IgGI ≥1:800	Endocarditis according to the modified Duke criteria
Landais [7]	France; 1985	IgGII ≥1:200 and IgMII ≥1:50 (in-house IFA), and evidence of seroconversion for specific antibodies	Suggestive symptoms of AQ, including history of fever, hepatitis, or atypical pneumonia	NA	NA	IgGI ≥1:800	Endocarditis based on the modified Duke criteria
Ayres [26][a]	UK; 1989	PhII >1:256 or >fourfold rise in titre at the time of outbreak (CFT)	Recent fever or pneumonia	NA	NA	NS	Endocarditis
Marmion [29][a]	UK; 1989	≥Fourfold increase in titre to phII antigen or phII ≥1:256 in a convalescent serum sample or at the time of outbreak (CFT)	Compatible clinical illness	NA	NA	NS	Endocarditis (probable)
Kováčová [27]	Slovakia; 1993	Seroconversion or fourfold rise of phII or IgM (tests not specified; MIF [9] (CO 1:32), EIA (pos: absorbency ≥ mean of 30 neg sera plus 3 SDs), CFT (CO 1:16), MA (CO 1:16))	Subjective complaints	NA	NA	PhI ≥1:200 (CFT) and an elevated phII response, or IgG ≥1:800 (MIF)	NS

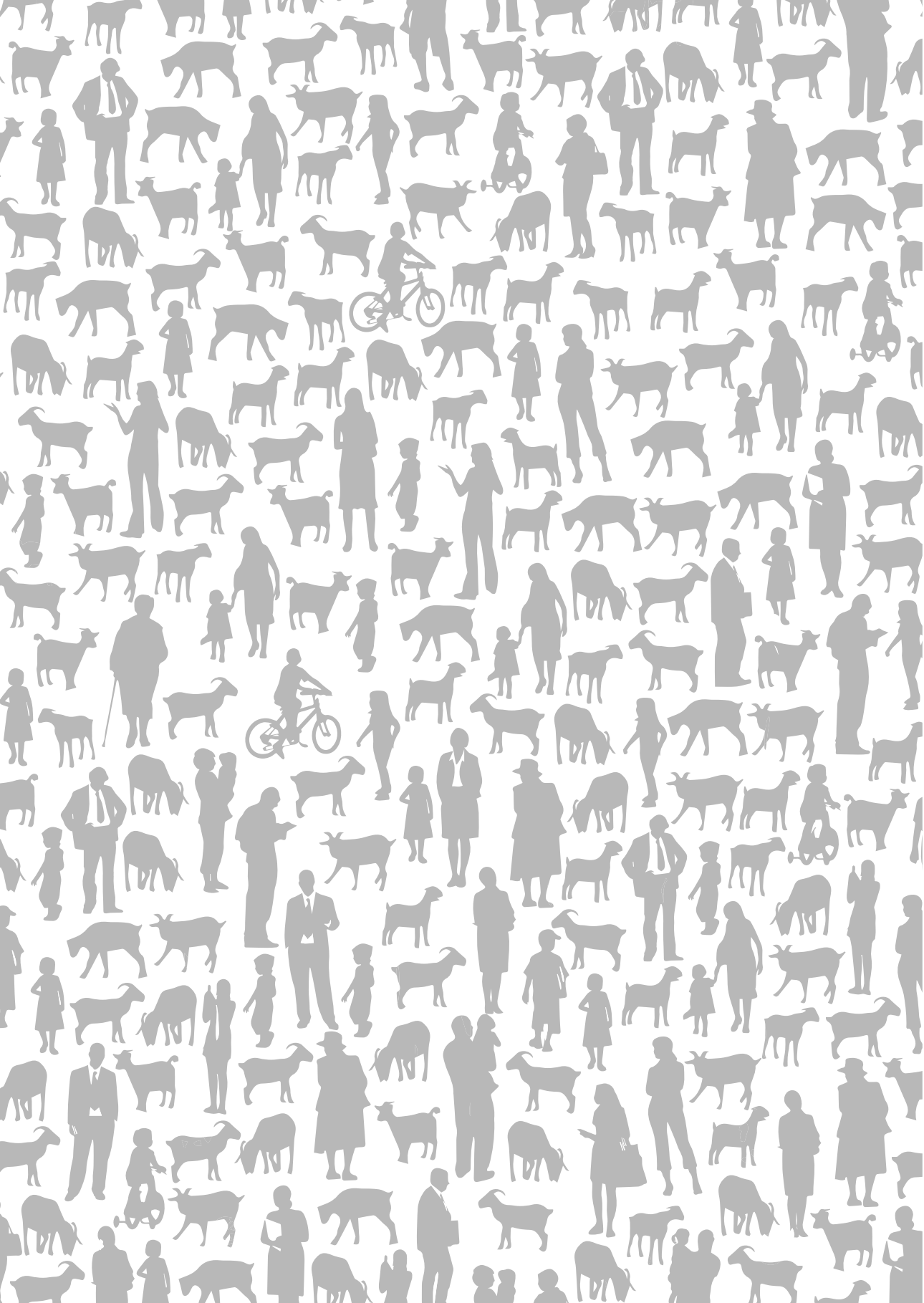
Ref.	Country; start study period	Definition acute Q fever		Definition past-resolved Q fever		Definition chronic Q fever / high titre	
		Serology	Clinical	Serology	Clinical	Serology	Clinical
Hussain-Yusuf [25]	UK; 2002	Confirmed AQ during the 2002 Q fever outbreak in Newport, UK (IgMII >1:320 (IFA), or fourfold rise (CFT), or IgMII 1:20−1:160 and IgGII >1:320) [44]	Symptoms compatible with AQ	NA	NA	IgGI ≥1:800	Endocarditis according to the modified Duke criteria [45]
Tissot-Dupont [8][b]	France; 2002	IgGII ≥1:100 and/or IgMII ≥1:25 (in-house IFA)	NCSI	NA	NA	IgGI ≥1:800	NCSI
Wagner-Wiening [16][b]	Germany; 2003	PhII IgM ELISA (Serion\Virion)	NCSI	NA	NA	IFA phI >1:512 (BIOS, Germany)	NCSI
Hung [12]	Taiwan; C1: 2004, C2: 2009	IgMII >1:80 in any acute phase serum sample or fourfold increase of IgGII between paired acute and convalescent phase serum samples (IFA, Focus Diagnostics)	NCSI	NA	NA	IgGI ≥1:800	Symptoms suggestive of chronic Q fever
Limonard [13]	the Netherlands; 2007	Seroconversion or fourfold increase of antibody titre (CFT, Serion\Virion) in samples taken ≥14 days apart, or presence of both IgMII and IgGII (IFA, Focus Diagnostics, CO 1:64), or a pos serum PCR	≥1 compatible clinical symptoms: fever, fatigue, chills, headache, myalgia, sweats, cough	NA	NA	IgGI ≥1:800, for ≥6 months after the initial day of illness	Endocarditis, vascular infection, osteoarticular infection, chronic hepatitis, pregnancy
van der Hoek [15]	the Netherlands; 2007	Both IgMII and IgGII ≥1:32 (IFA, Focus Diagnostics) or pos PCR result preceding seroconversion in IFA	NCSI	NA	NA	Presence of at least 2 of the following 3 criteria: (1) IgGI ≥1:1,024, (2) pos PCR ≥3 months after AQ, and (3) clinical or radiological signs interpreted by a medical specialist as highly suggestive of CQ	NS
Hartzell [31]	US; NR	Specific CO and reference ranges vary between laboratories (IFA, Focus Diagnostics)	Clinical syndromes consistent with AQ	NA	NA	IgGI ≥1:1,024	Fever, chills, weight loss, shortness of breath, new heart murmur, elevated inflammatory markers

Ref.	Country; start study period	Definition acute Q fever		Definition past-resolved Q fever		Definition chronic Q fever / high titre	
		Serology	Clinical	Serology	Clinical	Serology	Clinical
Fournier [10]	France; 1995	NA	NA	NA	NA	IgGI ≥1:800 and IgGI ≥ IgGII (in-house IFA), and/or when the bacterium was isolated or PCR-amplified from a biopsy sample of an aneurysm or vascular graft	NCSI
Kampschreur [19]	the Netherlands; vascular 2009, valvular 2010	NA	NA	Seropositive: any IgGII ≥1:128 (IFA, Focus Diagnostics)	NCSI	NA	NA
Kampschreur [20]	the Netherlands; 2010	NA	NA	IgGI <1:1,024 and neg PCR (IFA, Focus Diagnostics)	NCSI	Probable CQ: IgGI ≥1:1,024; proven CQ: pos *CB* PCR result on blood or tissue in combination IgGI ≥1:1,024	NCSI
Wegdam-Blans [21]	the Netherlands; 2010	NA	NA	IgGII ≥1:32 and IgGI <1:1,024 and neg PCR (IFA, Focus Diagnostics)	NCSI	IgGI ≥1:1,024 and/or pos PCR, based on the recently published document of the Dutch Q fever consensus group [34] for the diagnosis of CQ	NCSI

AQ: acute Q fever; CFT: complement fixation test; CO: cut-off; CQ: chronic Q fever; EIA: enzyme immunoassay; HT: high titre; IFA: indirect immunofluorescence assay; IgGI: anti-phase IgG I titre; IgGII: anti-phase IgG II titre; IgMII: anti-phase IgM II titre; MIF: micro-immunofluorescence; NA: not applicable; NCSI: no clinical signs included; neg: negative; NS: not specified; NR: not reported; ph: phase; pos: positive; SD: standard deviation.

[a] Data focusing on Q fever fatigue syndrome (QFS) are not included in this systematic review.

[b] Includes follow-up of known acute Q fever cases and screening of high-risk groups in order to detect asymptomatic or unknown *C. burnetii* infections.



Chapter 5

POPULATION SCREENING FOR CHRONIC Q-FEVER SEVEN YEARS AFTER A MAJOR OUTBREAK

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ABSTRACT

Introduction

From 2007 through 2010, the Netherlands experienced a large Q-fever epidemic, with 4,107 notifications. The most serious complication of Q-fever is chronic Q-fever.

Methods

In 2014, we contacted all 2,161 adult inhabitants of the first village in the Netherlands affected by the Q-fever epidemic and offered to test for antibodies against *Coxiella burnetii* using immunofluorescence assay (IFA) to screen for chronic infections and assess whether large-scale population screening elsewhere is warranted.

Results

Of the 1,517 participants, 33.8% were IFA-positive. Six IFA-positive participants had an IgG phase I titre ≥1:512. Two of these six participants were previously diagnosed with chronic Q-fever. Chronic infection was diagnosed in one of the other four participants after clinical examination.

Conclusions

Seven years after the initial outbreak, seroprevalence remains high, but the yield of screening the general population for chronic Q-fever is low. A policy of screening known high-risk groups for chronic Q-fever in outbreak areas directly following an outbreak might be more efficient than population screening. A cost-effectiveness analysis should also be performed before initiating a population screening program for chronic Q-fever.

INTRODUCTION

Q-fever is a zoonotic disease caused by the bacterial pathogen *Coxiella burnetii (C. burnetii)* [1, 2]. From 2007 through 2010, the Netherlands experienced a large Q-fever epidemic, with 4,107 notifications [3]. Prior to 2007, the seroprevalence of Q-fever antibodies among the Dutch general population was 2.4% [3]. In 2007, a sample of the inhabitants of Herpen—the first Dutch village affected by the Q-fever outbreak—had a seroprevalence rate of 25.1% [4].

The most serious complication of Q-fever is chronic Q-fever. Chronic Q-fever develops in 1.5-2% of Q-fever infections and can be detected months—or even years—after the initial infection, which was either symptomatic or asymptomatic [5]. The risk factors for chronic Q-fever include pre-existing cardiac valvulopathy, vascular graft, aneurysm, and immunosuppression [5]. Chronic *C. burnetii* infection can lead to endocarditis, an infected aneurysm or vascular graft, causing high morbidity and mortality even if optimal treatment is received [1, 6]. Because chronic Q-fever is not classified as a notifiable disease, precise numbers are not available; however, up to May 2012, 284 patients were voluntarily registered into a database as part of a research project run by the University Medical Center Utrecht [7]. For early detection of chronic Q-fever, patients should have at least one serological examination within one year following the acute infection [8]. The serological follow-up screening of acute Q-fever patients varies widely among regions, ranging from 25% to 95% [9].

General practitioners (GPs), inhabitants of regions with a high Q-fever incidence and the Dutch national Q-fever patient organization, speculated that the number of chronic Q-fever cases of the 2007-2010 epidemic was underestimated. Chronic Q-fever was incidentally diagnosed years after asymptomatic infection but the extent was never quantified. Therefore, seven years after the initial outbreak in the Netherlands, we measured the serological *C. burnetii* status of inhabitants of the high incidence village Herpen in order to identify chronic Q-fever infections and assess whether large-scale population screening elsewhere is warranted.

METHODS

The Municipal Health Service (MHS) "*GGD Hart voor Brabant*" performed this study as part of the larger Q Herpen II project. The Medical Ethics Review Committee of the University Medical Center Utrecht approved the study (protocol 13-367/D Q Herpen II).

For this cross-sectional population study, all adult inhabitants (≥18 years of age) of the village of Herpen (Dutch postal code 5373) were invited to participate. The municipal administration provided demographic data for these 2,161 inhabitants. In January 2014, all inhabitants were sent an information package by post, including information regarding the

study, a request to participate, a questionnaire, an informed consent form, and a laboratory form for venipuncture.

The questionnaire included questions regarding demographics, smoking history, risk factors associated with chronic Q-fever, history of Q-fever infection and vaccination. Answers to questions about general health status, initial symptoms, chronic medical conditions, and medication use are currently being analysed in other sub-studies.

During five days in February and one day in March 2014, participants provided their written informed consent to participate in this study with the questionnaire. Informed consent forms and questionnaires were checked for missing information and errors by medical staff and the participant, followed by a venipuncture.

Diagnosis

Antibodies against *C. burnetii* were measured using immunofluorescence assay (IFA) see Supplementary Information (SI) S1 Text., and an IgG phase I or II titre ≥1:64 was interpreted as IFA-positive.

The Dutch Q-fever Consensus Group [10] considers an IgG phase I titre ≥1:1024 an indication of possible chronic Q-fever; for a definitive diagnosis, a comprehensive medical examination is required. In our study, given the lack of an initial clinical examination, the serological cut-off value was set one dilution lower (at IgG phase I 1:512) in order to maximize sensitivity.

Participants with an IgG phase I titre ≥1:512 were tested further using the Q-fever polymerase chain reaction test (PCR) S1 Text., and referred to the Q-fever clinic at Radboud university medical center (Radboudumc) for clinical examination, including echocardiography and positron emission tomography-computed tomography (PET-CT) [10], when deemed necessary.

The IFA results were reported to the participants and their GP together with a medical recommendation.

Previous infections

The IFA test results of this study in 2014 were compared with those obtained in 2007. The 2007 and 2014 studies were performed in the same village (Herpen) and used the same laboratory tests and cut-off values [4]. Data regarding previous Q-fever infections and notifications were obtained from the MHS.

Data analysis

Questionnaires were digitally scanned and analysed using SPSS 21.0. The age and gender of the non-responders were obtained from the municipal administration data. Proportions were compared using the chi-square test. Differences with $p<0.05$ were considered to be significant (two-tailed analysis). The independent sample t-test was used to calculate means.

RESULTS

The study population

Both a blood sample and a completed questionnaire were provided by 70.2% (n=1,517/2,161) of the adult inhabitants of Herpen, the Netherlands. The characteristics of the participants are summarised in Table 1.

Participants and non-participants were similar with respect to age (p=0.31) and gender (p=0.35). The mean age of participants and non-participants was 51.9 years (SD: 16.5 years) and 51.2 years (SD: 21.9 years), respectively. More participants with Q-fever (n=51/1,517) were notified by the MHS compared to non-participants with Q-fever (n=2/644; p<0.01).

Prevalence of antibodies against *C. burnetii*

Of the 1,517 participants, 513 (33.8%) tested positive for antibodies against *C. burnetii* (i.e., were IFA-positive; for titres see S1 Table.). Three of the 513 IFA-positive participants became seropositive after receiving a Q-fever vaccination in 2011; two other vaccinated participants were seronegative in 2014. The IFA-positive and IFA-negative participants were similar with respect to age, gender and education level. A risk factor for being IFA-positive was current smoking (OR 1.4; 95% CI: 1.05-1.80; p=0.02) versus former smoker and never smoked.

Of the 513 IFA-positive participants, six (1.2%) had an IgG I ≥1:512, Table 2 and a negative Q-fever PCR test. Two of these six participants were diagnosed previously with chronic Q-fever. The remaining four (two with an IgG phase I 1: 512) were referred for a comprehensive clinical examination; three of these participants had no evidence of a chronic *C. burnetii* infection and one participant-a male over the age of 65, with an increased erythrocyte sedimentation rate and a history of renal insufficiency, and diabetes mellitus type 2- was diagnosed with chronic Q-fever. This participant presented with a cardiac murmur, and although transoesophageal echocardiography revealed no signs of endocarditis, he was placed on a treatment regimen consisting of doxycycline (200 mg qd) and hydroxychloroquine (200 mg tid).

Of the 69 individuals with known cardiovascular risk factors, 16 (23.2%) were IFA-positive Table 1; three of the 16 participants previously received the Q-fever vaccine, and the other 13 were exposed to Q-fever naturally. Of these 13 participants two (15.4 %) developed a chronic infection. These were the two participants (out of the six with an IgG I ≥1:512) previously diagnosed with chronic Q-fever.

Comparison of the 2014 IFA test results with previous Q-fever tests

In 2007, 25.3% (111/443) of sampled adult inhabitants in Herpen were IFA-positive. We compared results from 287 individuals who participated in both studies and gave their consent to compare their data. Of the 204 IFA-seronegative participants in 2007, 36 (17.6%) were IFA

seropositive in 2014; these participants presumably became infected after 2007. Of the 83 seropositive participants in 2007, 14 (16.9%) tested negative in 2014.

Analysis of the data collected from the MHS, microbiological laboratories, and the Herpen 2007 study revealed that 24.9% of the IFA-positive participants in 2014 (n=128/513) previously tested positive. Although the laboratories informed the MHS of these 128 infections (because acute Q-fever is a notifiable disease), 78 (60.9%) of these cases did not meet the national notification criteria. Of the 513 positive participants in 2014, 51 (9.9%) had been notified previously by the MHS.

Table 1. Characteristics of the study participants.

	All		**IFA-positive**		**IFA-negative**		
	n=1,517	***(100%)***	**n=513**	***(33.8%)***	**n=1,004**	***(66.2%)***	***p*-value**
Mean age, years[1]	51.9	(SD 16.5)	51.6	(SD 15.7)	52.1	(SD 16.9)	0.58
Gender[2]							0.70
Male	752	*(49.6)*	258	*(50.3)*	494	*(50.8)*	
Female	765	*(50.4)*	255	*(49.7)*	510	*(49.2)*	
Smoking[2]							0.02
Current	276	*(18.3)*	110	*(21.4)*	166	*(16.6)*	
Former	570	*(37.7)*	194	*(37.8)*	376	*(37.6)*	
Never	666	*(44.0)*	209	*(40.8)*	457	*(45.8)*	
Education level[2,3]							0.25
Low	825	*(55.2)*	290	*(57.3)*	535	*(54.1)*	
Average	425	*(28.4)*	149	*(29.4)*	276	*(27.9)*	
High	245	*(16.4)*	67	*(13.2)*	178	*(18.0)*	
All cardiovascular risk factors[4]	93		22		71		
One or more cardiovascular risk factors	69		16		53		
Aneurysm	19	*(20.4)*	8	*(36.4)*	11	*(15.5)*	
Aortic bifurcation prosthesis	2	*(2.2)*	0	*(0.0)*	2	*(2.8)*	
Stent graft	40	*(43.0)*	6	*(27.3)*	34	*(47.9)*	
Tube graft	1	*(1.1)*	1	*(4.5)*	0	*(0.0)*	
Bypass	20	*(21.5)*	3	*(13.6)*	17	*(23.9)*	
Heart valve surgery	11	*(11.8)*	4	*(18.2)*	7	*(9.9)*	

[1]Independent sample *t*-test, [2]Pearson's chi-square test. For the purpose of the analysis current smoking was compared with past and never smoked and for education level low was compared with average combined with high. [3]Education level: low, ranging from no education to vocational training; average, ranging from secondary vocational education to preparatory academic training and high, higher professional and/or university education. [4]The *p*-value was not calculated for this heterogeneous group

Table 2. Summary of the six participants with an IgG I titre ≥1:512 and Q-fever status after clinical examination.

Patient	IgG phase I	IgG phase II	Gender	Age*	Initial symptoms	Year diagnosis Q-fever	Underlying disease	Chronic Q-fever diagnosed
1	1:512	1:4096	female	<65	yes	2007	None	no
2	1:512	1:4096	male	<65	no	2014	None	no
3	1:1024	1:1024	female	≥65	no	2014	Diabetes mellitus type II	no
4	1:1024	1:2048	male	≥65	yes	2008	Aneurysm + stent	yes, 2008
5	1:1024	1:2048	male	≥65	yes	2010	Heart valve surgery	yes, 2011
6	1:1024	1:4096	male	≥65	no	2014	Diabetes mellitus type II Impaired renal function	yes, 2014

*The age is not shown as the exact age of the participant as this could compromise the privacy of the individual. Participants 1, 2, 3, and 6 were due this study referred for a comprehensive clinical examination to exclude chronic Q-fever. Participant number 4, 5 and 6 were diagnosed with chronic Q-fever; number 4 after the development of an aneurysm, number 5 during screening before vaccination of high risk groups and, number 6 as a consequence of screening during the current study.

DISCUSSION

Seven years after a national Q-fever outbreak in the Netherlands, screening of 1,517 adults in one Dutch village revealed 33.8% seropositive participants and six participants with an IgG I titre ≥1:512. Two of these six participants were previously identified as having chronic Q-fever. Clinical evaluation of the remaining four individuals revealed one new chronic infection in a patient who had no prior history of acute Q-fever, no known cardiovascular risk factors, and no symptoms associated with an acute episode.

Prevalence of Q-fever

To the best of our knowledge, this is the first large-scale seroprevalence study conducted in an entire village in order to identify patients with chronic Q-fever. The seroprevalence of antibodies against *C. burnetii* in our study (33.8%) is higher than the 12.2% reported among blood donors from high-incidence areas [5]. Lower and higher [11] IFA cut-off values are used for screening. Lacking an international standard we used the value commonly used in the Netherlands. Because the village population presumably was exposed to *C. burnetii* from 2007 through 2010, we expected to find evidence of waning immunity in 2014. Our finding that 16.9% participants seroreverted from IFA-positive to IFA-negative is consistent with a study in Wales that reported a serorevertion rate of 18% after six years [12]. Thus, our 2014 test results are likely an underestimation of the actual number of infections that occurred during the outbreak.

A recent study conducted among blood donors from high-incidence areas concluded that each notification might actually represent ≥12 infections [13]. In our study, 9.9 % of IFA–positive participants were notified, confirming that the number of infections is approximately ten-fold greater than the number of notifications. Because these results were obtained from a village in which both the GPs and the general public are highly aware of Q-fever, we expect that even more infections went undiagnosed in other regions. Such underreporting is due primarily to asymptomatic infections, symptomatic but undiagnosed infections, and infections that do not meet our national notification criteria.

We found that 0.6% of seropositive participants in our study population developed chronic Q-fever, which is a lower rate than the 1.5–2% reported in the literature [5, 6]. Serological testing within one year detects 98% [14] of the patients at risk for developing chronic Q-fever. However, the incubation time for chronic Q-fever is unknown and without further serological and clinical investigation can present years or even decades later [15].

Strengths and limitations of the study

The primary strengths of our study are the large sample size, the high response rate (70.2% of the entire adult population in Herpen), the relative homogeneity of the study population, and the similarity between participants and non-participants. A limitation of our study is the possibility that individuals developed chronic Q-fever earlier and died without being diagnosed. It cannot be excluded that those with severe disease were unable to participate, moved or also died since the outbreak. We have no information on non-participants and their Q-fever status. We cannot exclude that one or more non-participants have chronic Q-fever. We cannot exclude potential bias caused by non-participation. Seropositive individuals could have been over represented if they desired to know their serological status because of certain risk factors. On the other hand they could have been under represented as they knew their long-term status due to serological follow-up. Those with an unknown Q-fever status or with a perceived risk for example occupational might have shown increased interest in the study. Furthermore we could only contact those who were registered by the municipality but we expect the number of unregistered inhabitants to be very low.

Conclusions

The Q-fever seroprevalence rate found in our study was remarkably high (34%), and 15% of the infected participants with at least one cardiovascular risk factor developed a chronic infection. Although our study revealed one new individual with chronic Q-fever, it is unlikely that screening other communities for chronic infections—particularly communities that were not as heavily exposed to *C. burnetii* during the outbreak—would yield significantly more infections. A policy of screening known high-risk groups for chronic infections in outbreak areas following an outbreak [8] might be more efficient and should be implemented rather

than *ad hoc* population screening. A cost-effectiveness analysis should also be performed before initiating a population screening program for chronic Q-fever.

ACKNOWLEDGEMENTS

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APPENDIX SUPPLEMENTARY INFORMATION

S1 Table. IFA test results of 1517 participants.

IgG Phase I	IgG Phase II	n	(%)
	Negative test results	**1004**	**(66.2)**
<1:64	<1:64	1004	
	Positive test results	**513**	**(33.8)**
<1:64	1:64	5	
<1:64	positive*	402	
<1:64	1:256	1	
1:64	<1:64	1	
1:64	1:64	4	
1:64	positive	13	
1:64	1:128	2	
1:64	1:256	8	
1:64	1:512	9	
1:64	1:1024	1	
1:64	>1:1024	2	
1:128	1:128	4	
1:128	1:256	5	
1:128	>1:256	1	
1:128	1:512	11	
1:128	1:1024	10	
1:128	>1:1024	10	
1:256	>1:256	3	
1:256	1:256	2	
1:256	1:512	3	
1:256	1:1024	3	
1:256	>1:1024	4	
1:256	1:2048	3	
1:512	***1:4096***	***2***	
1:1024	***1:1024***	***1***	
1:1024	***1:2048***	***2***	
1:1024	***1:4096***	***1***	

*Positive means a titer ≥1:64. The sample was however not titrated as phase I was not higher than 1:64. This made titration-in order to detect chronic Q-fever- unnecessary. The six potential chronic cases are shown in bold italics.

S1 Text. Laboratory material and methods

Immunofluorescence Assay

The IFA assay used for this study is from a commercially available kit of Focus diagnostics, Cypress, CA, USA.

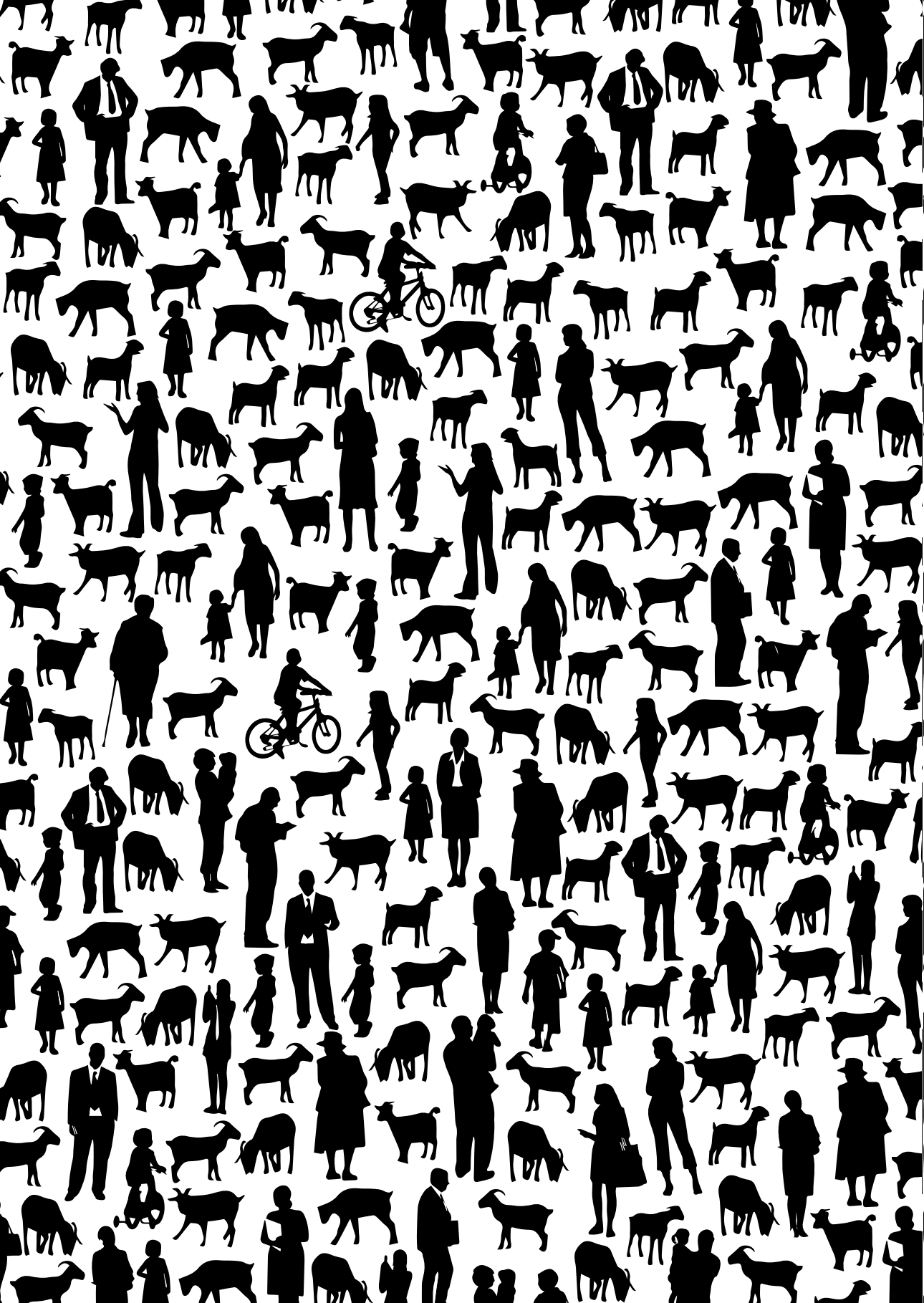
The area is post epidemic. In the Netherlands the cut-off of 1/64 is used. Some studies even use a cut off of 1/32. We compared the findings of 2007 and 2014 – similar cut off values and have no reasons to suspect that our cut off was to low. On the contrary one could argue that years after an outbreak the even lower titre of 1/32 might be used as anti-bodies might be weaning and past infections could be missed. As this low titre is one step away from a negative finding we found that titre to low and could lead to false sero positives. As the aim of the study was not to determine the correct or best cut off value for detecting a past infection it is not discussed in the concluding section of the manuscript. I do hope that the explanation given above does suffice without changing the conclusion especially as we are only allowed 2,000 words in this brief report.

Q-fever polymerase chain reaction

We used serum samples for the Q-fever polymerase chain reaction (PCR) test.

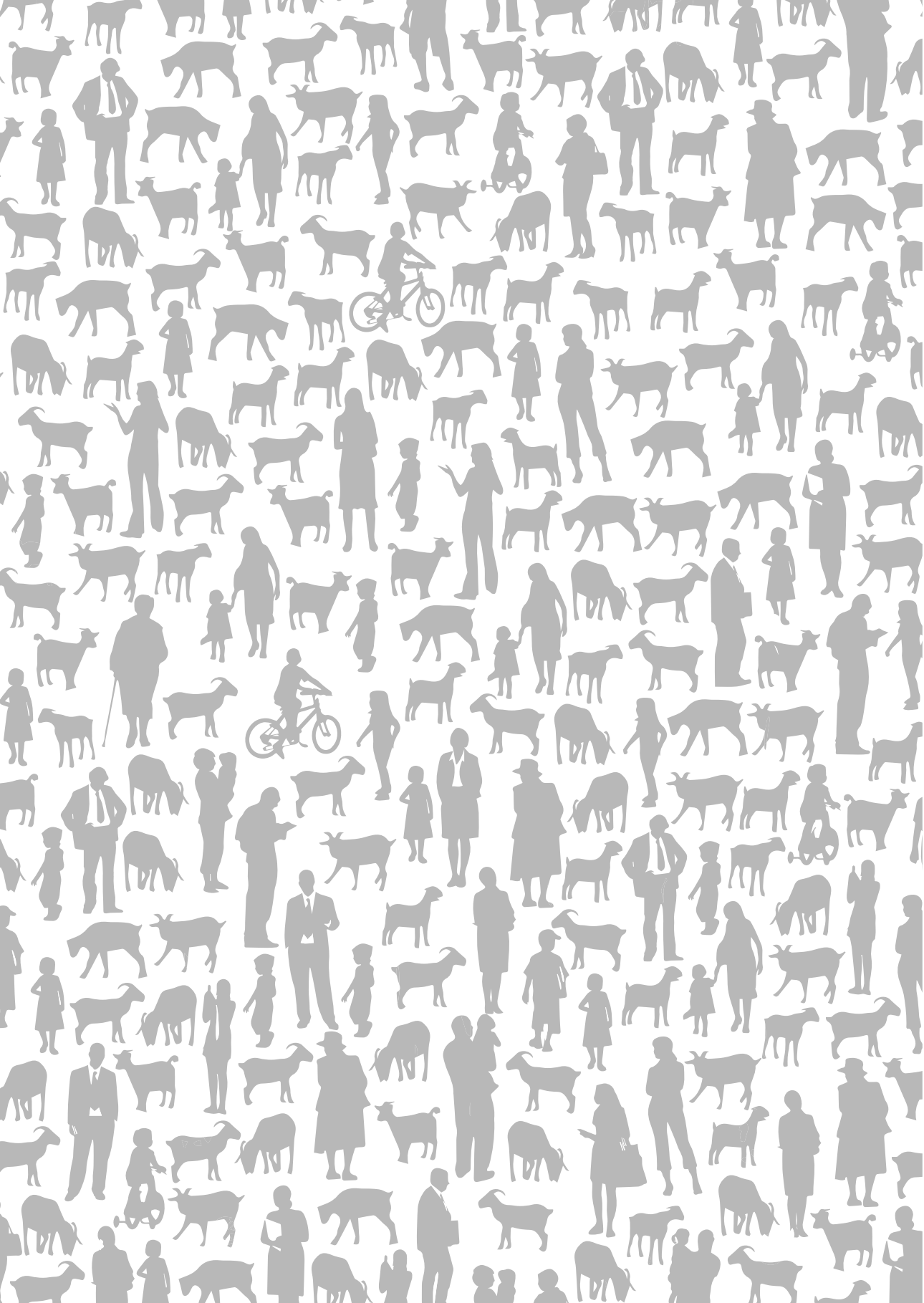
The gene targeted for the Q-fever polymerase chain reaction (PCR) test is the insertion element IS1111 of the *C. burnetii* genome of the Nine Mile strain. More information can be found in the article:

Schneeberger PM., Hermans MH, van Hannen EJ, Schellekens JJ, Leenders AC, Wever PC. Real-time PCR with serum samples is indispensable for early diagnosis of acute Q fever. Clinical and Vaccine Immunology, 2010 17(2), 286-290. http://cvi.asm.org/content/17/2/286.short



PART II

THE HEALTH STATUS ESPECIALLY FATIGUE AND WORK AFTER A C. BURNETII INFECTION



Chapter 6

SELF-REPORTED SICK LEAVE AND LONG-TERM HEALTH SYMPTOMS OF Q-FEVER PATIENTS

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ABSTRACT

Background

In the Netherlands, 1,168 Q-fever patients were notified in 2007 and 2008. Patients and general practitioners (GPs) regularly reported persisting symptoms after acute Q-fever, especially fatigue and long periods of sick leave, to the public health authorities. International studies on smaller Q-fever outbreaks demonstrate that symptoms may persist years after acute illness. Data for the Dutch outbreaks were unavailable. The aim of this study is to quantify sick leave and long-term symptoms after acute Q-fever.

Methods

Our study targeted 898 acute Q-fever patients, notified in 2007 and 2008 residing in the Province of Noord-Brabant. Patients from the 2008 cohort were mailed a questionnaire at 12 months and those of the 2007 cohort at 12-26 months after onset of illness. Patients reported underlying illness, Q-fever related symptoms and sick leave.

Results

The response rate was 64%. Forty percent of working patients reported long-term (>1 month) sick leave. Pre-existent heart disease odds ratio (OR) 4.50; confidence interval (CI) 1.27-16.09), hospitalisation in the acute phase (OR 3.99;95% CI 2.15-7.43) and smoking (OR 1.69; 95% CI 1.01-2.84) were significant predictors for long-term absence. Of the patients who resumed work, 9% were, at the time of completing the questionnaire, still unable to function at pre-infection levels due to fatigue or concentration problems. Of the respondents 40% reported persisting physical symptoms at the time of follow-up. Fatigue (20%) was most frequently reported. Daily activities were affected in 30% of cases.

Conclusions

Q-fever poses a serious persisting long-term burden on patients and society.

INTRODUCTION

Q-fever is a worldwide zoonotic disease caused by *Coxiella burnetii* (*C. burnetii*), an obligate intracellular bacterium. In the Netherlands, Q-fever was uncommon before 2007 with 10-20 notified cases annually [1]. Since 2007 and up to December 2010 more than 4.000 cases [2] were notified in four major outbreaks implicating dairy goats as the source [1,3-5]. Approximately 80% of the notified Q-fever patients reside in Noord-Brabant, the province with the highest dairy goat density in the Netherlands.

C. burnetii is common in a wide range of wild and domestic animals but only small ruminants, in particular sheep and goats, are associated with large human outbreaks [6,7]. Infected animals excrete billions of bacteria in birth products and to a lesser extent in faeces, urine and milk. Human infection occurs mainly after inhaling dust particles contaminated with *C. burnetii* [7].

In susceptible individuals infection develops after a mean incubation period of 21 days [6]. In general, 60% of the infected Q-fever patients are asymptomatic, whereas 20% of the patients develop mild symptoms. Another 20%, however, present with more severe symptoms ranging from high fever, severe headache, night sweating, nausea, diarrhoea, to pneumonia, hepatitis, pericarditis, myocarditis and neurological symptoms [8].

Chronic Q-fever may develop in up to 5% of acute cases [9-11], due to a reactivation of Coxiella. A follow-up of 686 Dutch acute Q-fever patients from 2007 to 2008 found that 1.6% converted to chronic Q-fever [12]. A feared presentation of chronic Q-fever is endocarditis [11] that may take 10-15 years to develop. Pregnant women and people with heart valve disorders, vascular prosthesis, or impaired immunity have a higher risk to develop a chronic infection.

Q-fever patients may develop Q-fever fatigue syndrome (QFS), a debilitating fatigue out of proportion with exertion that may last up to 10 years [13,14]. Post-infection fatigue [15] is not unique for Q-fever. It may also occur after other infectious diseases such as Lyme disease, Epstein–Barr virus infection [16], legionnaires disease [17], and other pneumonias [18].

Anecdotal information suggests that patients from the 2007 cohort had a more severe course of illness compared with those from the 2008 outbreak and were longer absent from work. However, evidence on the recovery of patients from the Dutch 2007 and 2008 cohorts is lacking. This study aims to fill that gap. The first objective is to assess the duration of sick leave after an episode of acute Q-fever-in 2007 or 2008-and the long-term self-reported symptoms and associated risk factors. The second objective is to asses differences between the two cohorts for the duration of self reported sick leave and the occurrence and frequency of long-term health symptoms.

METHODS

Study design and population

The population for this cohort study consisted of 898 patients notified in 2007 and 2008 to the Municipal Health Services 'Hart voor Brabant' and 'Brabant Zuid-Oost'. Due to incomplete data or an unknown month of onset of illness, 28 patients were excluded (Figure 1). The remaining 870 Q-fever patients fitted the Dutch notification criteria; a laboratory confirmation of Q-fever and clinical presentation with fever, pneumonia or hepatitis

Data collection

In February 2009, all patients received a study information folder including a participation request and consent form by post (Figure 1). Patients could state their willingness to take part in any of a number of studies under the so-called Q Quest-1 project, by signing and returning the consent form. Participating patients received a questionnaire-by postal mail-focussing on demographic characteristics, medical history, smoking behaviour, current Q-fever related physical symptoms and employment related items, such as duration of sick leave following acute Q-fever, resumption and current ability to work (employed, self-employed, volunteer work, household work). During a pre-test, the completion of the questionnaire took 20- 30 minutes.

All patients from the 2007 cohort received the questionnaire in February 2009 (13-26 months after onset of illness). Patients notified in 2008 were mailed a questionnaire one year after the month of onset of illness. Patients from both cohorts, received two reminders after three and six weeks. We obtained data on non-responders regarding gender, age, year of onset of disease and hospitalization from the notification data of the Municipal Health Services.

Data analysis

Questionnaires were double scanned and data were cleaned. Statistical analysis was done using SPSS 16 for windows. We used the Mantel–Haenzel Chi square and Fishers exact test to compare proportions. *P*-values are based on two tailed tests with a p-value<0.05 defined as significant. The notification data of the Municipal Health Services were used to compare responders and non-responders for age, gender, year of onset of illness and hospitalisation.

Multivariate logistic regression was used to model the relationship between outcome (sick leave >1 month or presence of symptoms) and the independent variables age, gender, hospitalisation, underlying diseases and year of onset of illness. Multivariate logistic regression was used to model the relationship between the determinants year of onset of illness and hospitalisation with the outcomes presence of symptoms (fatigue)and long-term sick leave. For the potential confounders, age, gender, smoking and co-morbidity , we used the same model.

RESULTS

Patient participation

The overall response rate was 63.9% (Figure 1). The mean time between the day of onset of illness and receiving the questionnaire was 19.5 months (SD 2.3) for patients of the 2007 cohort and 12.1 months (SD 0.5) for patients of the 2008 cohort. We were informed that five patients died, but had no information on the cause of death.

The response rate of men was lower than that of women as was that of younger (≤30 years of age) compared with older patients (> 30 years of age). There were no differences between responders and non-responders for year of onset of illness and hospitalization (see Supplementary Table S1 for details).

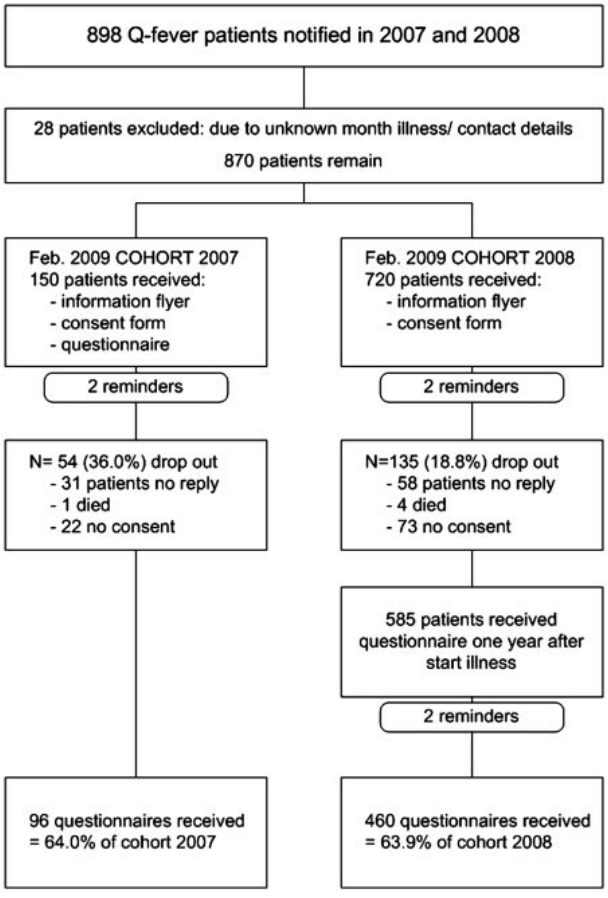

Figure 1.Response rate of patients from cohorts 2007 to 2008. Division in cohorts is on the basis of month of onset of illness.

Characteristics of the study population

The study population (Table 1) of the 2007 and 2008 cohorts was similar with respect to gender, age group, smoking behaviour and underlying diseases. The hospitalisation rate of patients of the 2007 cohort, however, was significantly higher [relative risk (RR) 2.50, 95% CI 1.68-3.01;*p*< 0.000] than that of the 2008 cohort. Patients from the 2007 cohort were more often depressed (OR 1.88, 95% CI 1.10-3.34; *p*= 0.044) than patients from the 2008 cohort.

Table 1. Characteristics of the study population (n= 556) of two cohorts (2007 and 2008) of acute Q-fever patients notified in The Netherlands.

Characteristics	Cohort 2007, n = 96 (%)	2008, n = 460	Total, n = 556	*p*-value
Gender				
Male	55 *(57.3)*	278 *(60.4)*	333 *(60.0)*	
Female	41 *(42.7)*	182 *(39.6)*	223 *(40.0)*	0.568
Mean age in years (SD)	50.4 *(14.9)*	51.8 *(13.3)*		
Smoker				
Yes	36 *(39.2)*	150 *(33.6)*	186 *(34.6)*	
No	56 *(60.8)*	296 *(66.4)*	352 *(65.4)*	0.317
Hospitalised				
Yes	42 *(43.8)*	89 *(19.5)*	131 *(23.7)*	
No	54 *(56.2)*	368 *(80.5)*	422 *(76.3)*	<0.000
Underlying disease[a]				
Yes	57 *(59.4)*	261 *(56.7)*	318 *(57.2)*	
No	39 *(40.6)*	199 *(43.3)*	238 *(42.8)*	0.639
Underlying diseases				
Diabetes	7 *(7.3)*	29 *(6.3)*	36 *(6.5)*	0.721
Heart disease	8 *(8.3)*	38 *(8.3)*	46 *(8.3)*	0.981
Lung disease	10 *(10.4)*	34 *(7.4)*	44 *(7.9)*	0.318
Arthritis	2 *(2.1)*	20 *(4.3)*	22 *(3.9)*	0.301
Depression	9 *(9.4)*	20 *(4.3)*	29 *(5.2)*	0.044
Other specified	4 *(4.2)*	40 *(8.7)*	44 *(7.9)*	0.158
Other unspecified	21 *(21.9)*	73 *(15.9)*	94 *(16.9)*	0.135

[a]Patients can state more than one underlying disease.

Sick leave

Prior to the Q-fever infection 62% of the study population was gainfully employed. During the episode of acute fever 91.3% of these patients reported sick for work (Figure 2). Overall 132 (39.6%) of study subjects that worked prior to the infection, were longer than one month (long-term sick leave) absent from work following an acute Q-fever infection. See Supplementary Table S2 for sick leave of the gainfully employed, volunteers and those who do household work.

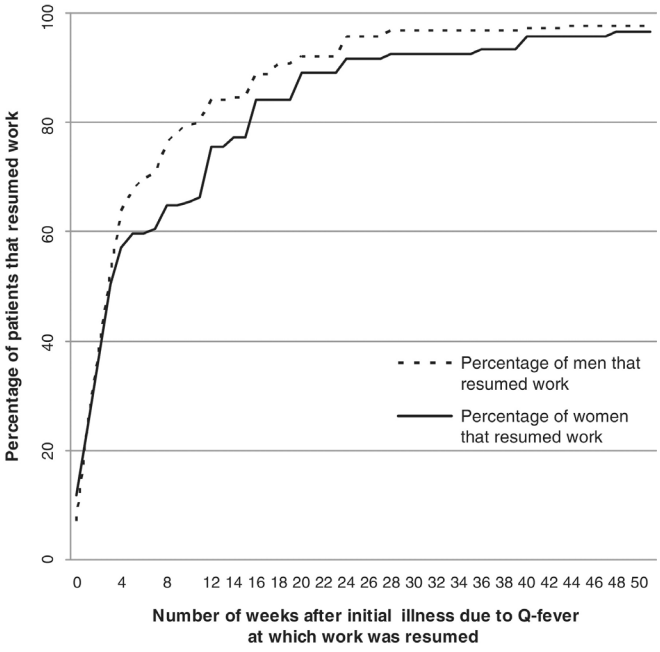

Figure 2. The week of self-reported work resumption following an epidode of acute Q-fever in 344 workers.

Hospitalisation, smoking and underlying heart disease were independent predictors for long-term sick leave (Table 2). Gender, age, year of onset of illness, underlying lung disease, depression or level of education were not significantly related to long-term sick leave (Table 2).

Self-reported symptoms

Almost 40% of patients reported at least one current health complaint at the time of follow-up that they perceived to be Q-fever related (Supplementary Table S3). The most frequently reported symptoms were: fatigue, 19.8%; difficulty concentrating, 9.5%; muscle pain, 9.0%; and night-time sweating, 7.9%. Women (OR 1.84, 95% CI 1.27-2.67; p= 0.001) were more likely to report symptoms than men. For fatigue this was 25.1% of women versus 16.2% among men.

The 2007 and 2008 cohorts were similar in number, type and frequency of reported symptoms (Supplementary Table S3). Multivariate logistic regression showed that year of onset of illness was not significantly related to the reporting of a health complaint, when controlling for differences in age, smoking, underlying heart/lung disease and depression. Women and patients that had been hospitalised or suffered depression were more likely to report fatigue at the time of follow-up (Table 2).

Table 2. Multivariate logistic regression analysis of risk factors for self-reported long-term fatigue measured at 12 to 26 months follow-up in 556 Q-fever patients and for sick leave (exceeding one month) in 334 paid workers after acute Q-fever.

	Long-term fatigue n= 110			Long-term sick leave n= 132		
Risk factor for	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Gender						
Female	1.77	(1.14- 2.75)	0.012	1.39	(0.83- 2.35)	0.213
Male (ref)						
Age [a]	1.01	(0.99- 1.03)	0.213	1.01	(0.97–1.03)	0.890
Hospitalization [b]						
Yes	1.95	(1.19- 3.19)	0.008	3.99	(2.15 – 7.43)	0.000
No (ref)						
Cohort						
2007	1.23	(0.71- 2.15)	0.461	1.18	(0.60 – 2.33)	0.626
2008 (ref)						
Smoking						
Yes	1.29	(0.79- 2.10)	0.299	1.69	(1.01- 2.84)	0.046
No (ref)						
Underlying Heart disease						
Yes	1.66	(0.79- 3.49)	0.182	4.51	(1.27-16.09)	0.020
No (ref)						
Underlying Lung disease						
Yes	1.61	(0.77- 3.33)	0.204	2.78	(0.93- 8.34)	0.068
No (ref)						
Depression						
Yes	2.53	(1.11- 5.76)	0.027	0.98	(0.23- 4.26)	0.976
No (ref)						

[a]Age has been modelled as a continues variable. [b]Hospitalization during the acute phase of illness.

Long term sick leave, resumption of work or daily activities in relation to perceived Q-fever related health symptoms

Study subjects (n= 132) 39.6% that were longer than one month (long-term sick leave) absent from work following an acute Q-fever infection showed more fatigue at 12-26 months after the initial illness than patients with a shorter sick leave period.

Of the patients that resumed work, 9.3% reported that they were unable to function at pre Q-fever levels at the time they completed the questionnaire, due to perceived Q-fever related health symptoms, mainly fatigue and concentration problems. Almost one third of patients (29.0% of the 2007 cohort and 33.1% of the 2008 cohort), reported that they had not fully resumed their daily activities at 12-26 months after onset of illness. Stated reasons were fatigue (80.8%) and respiratory problems (4.9%).

DISCUSSION

We analysed data from notifications and questionnaires of 556 Q-fever patients notified in 2007 and 2008 in the Netherlands. Our most important findings were that after an episode of acute Q-fever, two out of five patients were over a month absent from work. We found that hospitalisation in the acute phase, underlying heart disease and smoking behaviour were independent predictors for sick leave exceeding a month. Almost, one in ten patients were unable to function at pre Q-fever infection level at the time of the questionnaire mainly due to fatigue and concentration problems. Two out of five patients reported Q-fever related symptoms and one third indicated that they had not resumed their daily activities to the pre Q-fever infection level.

Work and sick leave

To our knowledge, this is the first time that data on Q-fever and sick leave following a Q-fever outbreak are presented. We are therefore unable to compare the results with other studies on Q-fever. We do, however, know that in the Netherlands the average duration of sick leave per employee was 6.3 days [19] in 2008. One in three Dutch patients with sick leave have a cold or flu like symptoms, but are rarely longer than one week absent from work [19]. In a large cross sectional study [20], 16% of Dutch employees reported more than 9 days sick leave per year. In our study 57% of Q-fever patients reported more than 9 days sick leave per year.

Patients that reported persisting fatigue at 12-26 months, were also significantly more often long-term absent from work due to sick leave following the acute infection. Our findings are in line with a study from Huibers, *et al* [21], that showed that persisting fatigue has a strong correlation with sick leave exceeding 42 days.

Symptoms

One to two years after acute Q-fever, two thirds of the patients still reported symptoms that they attributed to Q-fever. Cohorts did not differ in the overall reported symptoms and specific symptoms. We had expected to find a difference in symptoms between the cohorts as clinicians often reported that patients of the 2007 cohort had more serious illness. Due to methodological reasons (see under Methodological considerations and study limitations) we are unable to asses if the 2007 cohort initially had more symptoms during the convalescence period and partially recovered or that the level of persistent symptoms was similar for both cohorts.

Hatchette and Hayes [22] reported 51% of the Q-fever patients with persistent symptoms 26 months after the acute Q-fever episode. Ayres, *et al*. [14] studied a cohort of 71 Q-fever patients and found that five years after the initial infection up to 68% of study subjects pre-

sented with symptoms. Our findings are in line with these two studies. It may be questioned whether long-term persistence of symptoms is unique for Q-fever. In a study of patients with community acquired pneumonia (of varying degrees of severity) a full recovery was reported after 6-18 months. Persistence of symptoms was mostly attributed to morbidity that existed before the pneumonia episode [18]. In our study, patients with pre-existent heart or lung disease had similar outcomes for persisting symptoms than those without pre-existent disease.

Fatigue

In the present study, 19.8 % of the Q-fever patients report fatigue 12-26 months after the onset of illness, without a significant difference between both cohorts. Although patients from the 2007 cohort were more often hospitalised and our study shows that hospitalisation in the past-due to Q-fever is significantly related to fatigue 12-26 months later, it appeared that the year of onset of illness did not influence long-term fatigue.

In another study [23] on these same patients, we found that when using a validated instrument the Nijmegen Clinical Screening Instrument (NCSI) [24,25] up to 43.5% of patients stated fatigue. Other studies also report much higher rates of 52% [26] undue tiredness after one year, 51% up to five years later [14] or even 64% 10 years after a Q-fever infections [13]. We therefore suspect that the outcome is related to the way the information on fatigue is gathered.

Our finding that patients who reported fatigue had been more often hospitalised is in line with Hickie *et al.* [27] who report that the key risk factor for post-infective fatigue syndromes is the severity of the acute illness. In their study, they found no age, sex-related or psychological risk factors. We found, however, that women and patients with depression reported more fatigue. Depression has two components [28] a somatic factor often expressed as fatigue and a depression factor. The dominating factor may determine the diagnosis. In our study, we could not make a distinction between the two as we did not ask additional questions. Different co morbidities –including chronic fatigue-associated with depression can be explained by (neuro) inflammatory and oxidative and nitrosative stress path ways [29]. Unexplained fatigue and depression might act as independent risk factors of each other [30]. The question is whether the explainable fatigue caused by Q-fever might be a pre-curser to depression. The question is whether the explainable fatigue caused by Q-fever might be a pre-cursor to depression.

Women reported other symptoms significantly more often than men. This does not necessarily mean that women have more symptoms, as woman are known to present symptoms more often [31].

We did not medically examine patients and could not establish whether the fatigue fulfilled the diagnostic criteria of the chronic fatigue syndrome (CFS) [32, 33]. Nor did we have

information on the duration, the severity of the fatigue, the presence of tender lymph nodes or possible other causes.

Cohort comparison

Patients from the 2007 cohort received the questionnaire later (13 to 26 months after the acute episode) than those of the 2008 cohort (at 12 months). Therefore, data from the two cohorts are not entirely comparable as we are unable to assess the initial level of symptoms of the 2007 cohort.

The hospitalisation rate was much higher for the 2007 cohort (43.8%) than for the 2008 cohort (19.5%). This shows that our study population is in this respect a good representation of the notified Q-fever patients as mandatory notification data show that the hospitalisation rate for our area was 43.7% in 2007 and 16.3% in 2008. This is much higher than the rate of 2-3% reported in literature [34]. The high percentage of hospitalized patients in 2007 was largely influenced by active case finding in a retrospective survey among hospitalized cases [35]. Both patients and clinicians recognised and diagnosed Q-fever more readily in 2008 when it had become apparent that this previously uncommon disease presented more often in the area. Only the very ill patients might have been recognised and diagnosed by clinicians in 2007.

Although hospitalized patients reported more long-term fatigue and sick leave, we did not find an independent significant relation between cohort and reported fatigue or absence from work.

Methodological considerations and study limitations

A limitation of this study is that we lacked a control group. The reason was that this study was designed as a cost of illness study rather than an etiological study.

One of the complexities of this study is that we were dealing with many confounders such as age, gender and co-morbidity; for example heart disease, depression and health symptoms such as fatigue. Our determinants of interest were, however, hospitalisation and the year of onset of illness. In the absence of other data our data give a valuable insight into sick leave and symptoms related to Q-fever.

The response rate was significantly higher for woman and patients older than 30 years. This is in line with survey response rates in the Netherlands [36]. Due to this selection bias, the percentage of fatigue found in this study might be slightly higher than that in the total Q-fever population.

Access to pre-Q fever heath status and sick leave data would have been ideal but these data were unavailable. Therefore, we cannot proof if all reported sick leave and health symptoms are completely related to Q-fever.

In the absence of other data, our data give a valuable insight into sick leave and symptoms related to Q-fever. One could question whether these symptoms were caused by Q-fever because symptoms of Q-fever may not be very specific. By asking per symptom whether the symptom was present we might have prompted patients wich could have led to overreporting. The same could have applied for co-morbidity.

Although we asked questions on past or initial symptoms, we only analysed current symptoms thereby omitting problems with recall bias. For sick leave, we cannot exclude recall bias as we asked patients to recall their sick leave up to 26 months after an episode of acute Q-fever. Many patients were, however, very precise and even stated dates of sick leave. Although we asked patients about productivity loss at work we did not use a validated instrument and can therefore not directly compare our findings with other studies.

Data on sick leave were only available for responders. This might have biased the results on sick leave. Although we are not sure about that, we do have some indications about the validity of our findings. The strongest indication is that the hospitalisation rate, one of the most important determinants of the duration of sick leave, was similar for responders and non-responders.

Conclusions

The negative impact of Q-fever on productivity and perceived health status is considerable, especially when taking the high incidence in certain communities into account. Hospitalisation, as an indicator of severity of the acute illness, turned out to be a strong predictor for long-term sick leave and persistent fatigue in Q-fever patients.

This study demonstrates the considerable burden of disease from Q-fever for individual patients, families, and society.

ACKNOWLEDGEMENTS

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Key-points:

- After an episode of acute Q-fever, 40% of the working patients were longer than one month absent from work. Hospitalisation in the acute phase, underlying heart disease and smoking behaviour were independent predictors for sick leave exceeding a month.
- More than one year after an episode of acute Q-fever 9% of patients had not completely resumed work. Fatigue and concentration problems were the main reasons.
- One year after an episode of acute Q-fever, 40% of patients still report Q-fever related symptoms.
- More than 30% of our study population report that they have not resumed their daily activities to the pre Q-fever infection levels.

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APPENDIX SUPPLEMENTARY TABLES

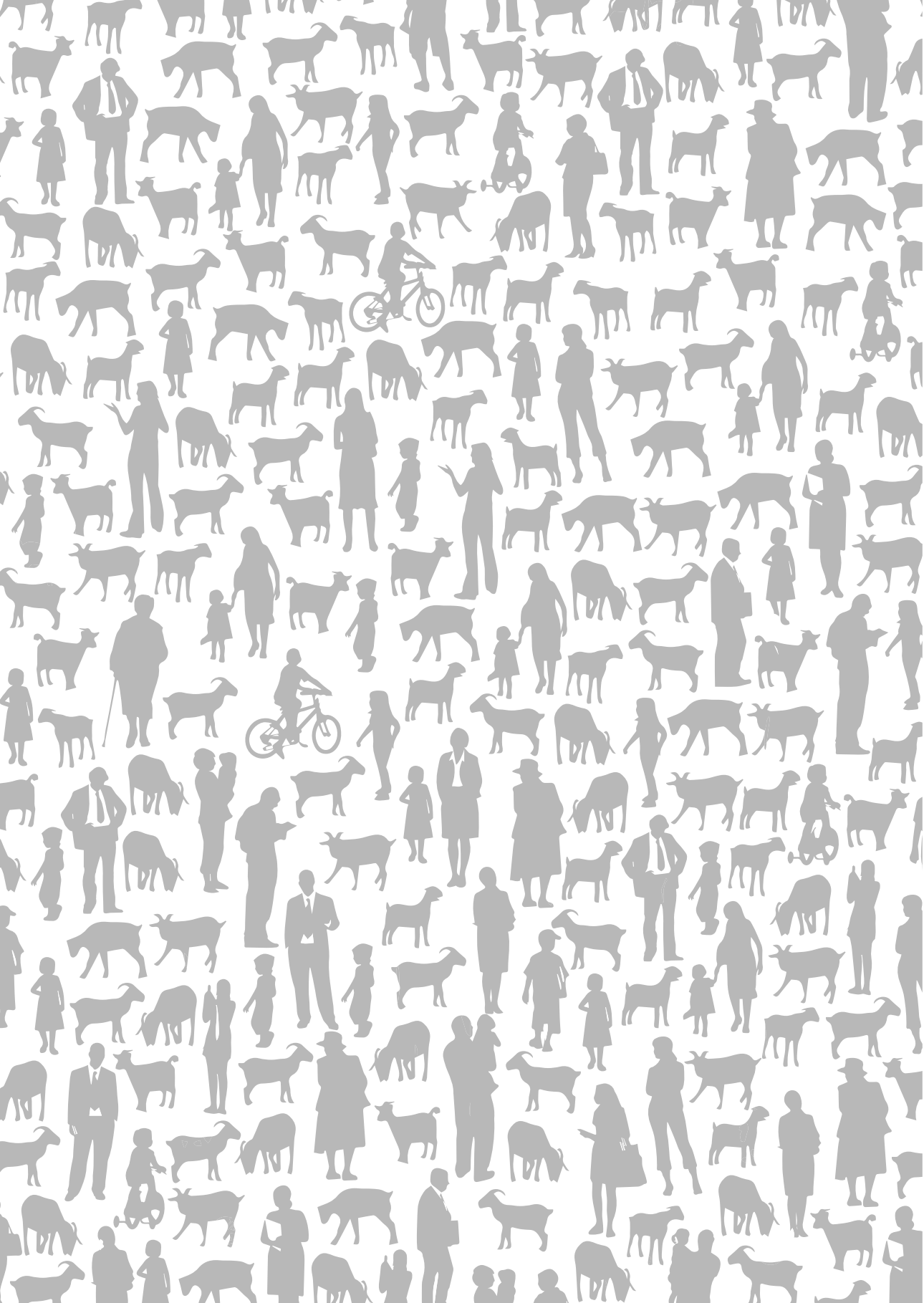
Table S1: Weeks of sick leave following acute Q-fever per type of work and year of onset of illness.

Type of work*	**Cohort 2007**		**2008**		**Totaal**	
Paid work	n=53		n= 281		n= 334	
Weeks sick leave						
Mean duration (SD)	11.4	*(15.1)*	7.3	*(9.9)*	7.9	*(11.0)*
Volunteer	n= 12		n= 48		n= 60	
Mean duration (SD)	10.1	*(18.8)*	7.5	*(11.3)*	8.0	*(12.9)*
Housekeeping	n= 43		n=190		N=233	
Mean duration (SD)	10.4	*(14.7)*	5.6	*(8.8)*	6.5	*(10.6)*

*Patients can state more than one work situation.

Table S2. Self-reported symptoms 12 to 26 months after an episode of acute Q-fever perceived to be attributed to Q-fever of two cohorts (2007 & 2008)* of acute Q-fever patients notified in the Netherlands.

	Cohort	2007	2008		Total	
Symptom /problem**	**n=93**	***(%)***	**n=444**	***(%)***	**n=537**	***(%)***
No	56	*(60.2)*	269	*(60.5)*	325	*(60.4)*
Yes	37	*(39.8)*	175	*(39.5)*	212	*(39.6)*
Fatigue	25	*(26.0)*	85	*(18.5)*	110	*(19.8)*
Poor concentration/memory	12	*(12.5)*	41	*(8.9)*	53	*(9.5)*
Muscle aches	9	*(9.4)*	41	*(8.9)*	50	*(9.0)*
Joint pain	7	*(7.3)*	39	*(8.5)*	46	*(8.3)*
Night time sweating	5	*(5.2)*	39	*(8.5)*	44	*(7.9)*
Breathing difficulty	6	*(6.2)*	36	*(7.8)*	42	*(7.6)*
Malaise	10	*(10.4)*	27	*(5.9)*	37	*(6.7)*
Chest pain or pressure	7	*(7.3)*	29	*(6.3)*	36	*(6.5)*
Headache	5	*(5.2)*	29	*(6.3)*	34	*(6.1)*
Stiff neck	10	*(10.4)*	24	*(5.2)*	34	*(6.1)*
Coughing	6	*(6.2)*	28	*(6.1)*	34	*(6.1)*
Skin rash	6	*(6.2)*	18	*(3.9)*	24	*(4.3)*
Eye problems	4	*(4.2)*	17	*(3.7)*	21	*(3.8)*
Stomach ache	4	*(4.2)*	13	*(2.8)*	17	*(3.1)*
Ear problems	3	*(3.1)*	13	*(2.8)*	16	*(2.9)*
Confusion	3	*(3.1)*	12	*(2.6)*	15	*(2.7)*
Nausea	4	*(4.2)*	9	*(2.0)*	13	*(2.3)*
Pain upper belly	1	*(1.0)*	11	*(2.4)*	12	*(2.2)*
Weight loss	3	*(3.1)*	8	*(1.7)*	11	*(2.0)*
Diarrhoea	3	*(3.1)*	6	*(1.3)*	9	*(1.6)*
Sore throat	0	*(0.0)*	7	*(1.5)*	7	*(1.3)*
Jaundice	1	*(1.0)*	2	*(0.4)*	3	*(0.5)*
Fever	0	*(0.0)*	2	*(0.4)*	2	*(0.4)*



Chapter 7

THE HEALTH STATUS OF Q-FEVER PATIENTS AFTER LONG-TERM FOLLOW-UP

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ABSTRACT

Background

In the Netherlands, from 2007 to 2009, 3,522 Q-fever cases were notified from three outbreaks. These are the largest documented outbreaks in the world. Previous studies suggest that symptoms can persist for a long period of time, resulting in a reduced quality of life (QoL). The aim of this study was to qualify and quantify the health status of Q-fever patients after long-term follow-up.

Methods

870 Q-fever patients of the 2007 and 2008 outbreaks were mailed a questionnaire 12 to 26 months after the onset of illness. We assessed demographic data and measured health status with the Nijmegen Clinical Screening Instrument (NCSI). The NCSI consists of three main domains of functional impairment, symptoms and QoL that are divided into eight sub-domains. The NCSI scores of Q-fever patients older than 50 years (n = 277) were compared with patients younger than 50 years (n = 238) and with norm data from healthy individuals (n = 65) and patients with chronic obstructive pulmonary disease (n = 128).

Results

The response rate was 65.7%. After applying exclusion criteria 515 Q-fever patients were included in this study. The long-term health status of two thirds of Q-fever patients (both younger and older than 50 years) was severely affected for at least one sub-domain. Patients scores were most severely affected on the sub-domains general QoL (44.9%) and fatigue (43.5%). Hospitalisation in the acute phase was significantly related to long-term behavioural impairment (OR 2.8, CI 1.5-5.1), poor health related QoL (OR 2.3, CI 1.5-4.0) and subjective symptoms (OR 1.9, CI 1.1-3.6). Lung or heart disease, depression and arthritis significantly affected the long-term health status of Q-fever patients.

Conclusions

Q-fever patients presented 12 to 26 months after the onset of illness severe-clinically relevant- subjective symptoms, functional impairment and impaired QoL. All measured sub-domains of the health status were impaired. Hospitalisation and co-morbidity were predictors for worse scores. Our data emphasise that more attention is needed not only to prevent exposure to Q-fever but also for the prevention and treatment of the long-term consequences of this zoonosis.

BACKGROUND

Q-fever is a worldwide zoonotic disease caused by *Coxiella burnetii* (*C. burnetii*), an obligate intracellular bacterium. Until 2007 Q-fever was uncommon in the Netherlands, with 5-20 notified cases annually [1]. From 2007-2009, 3,522 cases were notified in three large outbreaks [2], with dairy goats implicated as the source [1, 2]. The majority of Q-fever patients (80%) reside in the southern province of Noord-Brabant [1-3]. Between 2007 and early 2010 some hard-hit communities suffered a cumulative incidence of 2,650 notified Q-fever cases per 100,000 inhabitants (one in 38 people).

In general 60% of infected Q-fever patients are asymptomatic, while 20% develop mild symptoms [4]. The remaining 20% of Q-fever patients present with more severe symptoms ranging from high fever, severe headache, night sweating, nausea and diarrhoea, to pneumonia, hepatitis, pericarditis, myocarditis and neurological symptoms [5]. Chronic Q-fever may develop in 1.5-5% of acute cases, due to reactivation of *C. burnetii* [4, 6, 7]. A feared complication is endocarditis, which may take 10-15 years to develop. In particular pregnant women and patients with heart valve disorders, vascular prosthesis and impaired immunity have a higher risk to develop chronic infection [4, 6, 7]. Protracted fatigue up to 10 years after infection [8, 9] is another late sequel. A *Post-Infection Fatigue Syndrome* (PIFS) [9] may also occur after other infections such as Lyme disease [10]. In 10-15% of Q-fever patients fatigue can last up to 5-10 years [11] and is referred to as *Post Q-fever fatigue Syndrome* (PQFS). Other authors [8, 9] state higher percentages of fatigue. PQFS presents with symptoms resembling those of *Chronic Fatigue Syndrome* (CFS).

During the Dutch Q-fever outbreaks patients and general practitioners (GPs) repeatedly reported persisting symptoms to the public health authorities and in particular about fatigue. These signals could not be substantiated, as we lacked specific information on the health status at individual and at Q-fever patient population level. Furthermore, we were uncertain whether data from other small national [12] and international studies, would also apply to our large Dutch Q-fever cohorts. In order to assess the long-term health status of Dutch Q-fever patients we started this study.

Long-term health status impairment may have a large impact on patients, their families and the societies that they are part of. In this study, the primary aim was to provide a detailed assessment of the health status of Q-fever patients 12 to 26 months after the onset of illness. This information will assist clinicians and patients to better understand the natural course, consequences of the disease and predictors for an affected health status.

METHODS

Q-Quest I study

This cohort study is part of the collaborative Q-Quest I study, which aims to measure the impact of the Q-fever outbreaks in terms of population health and societal implications. The study started in May 2008 and includes studies on diagnostics, treatment, clinical symptoms, costs and the long-term health status.

Study design and population

Eligible for inclusion in this study were Q-fever patients notified in 2007 and 2008 to the Municipal Health Service "Hart voor Brabant" and "Brabant Zuid-Oost" with a first day of illness in 2007 or 2008. All patients fitted the Dutch notification criteria; a laboratory confirmation of Q-fever and clinical presentation of fever, pneumonia or hepatitis. Patients were diagnosed by 4 different laboratories. At the beginning of the outbreak in 2007 the laboratory test most frequently used was the CFT (complement fixation test). A sero-conversion or a fourfold increase in titre, between two subsequent tests with a minimum time interval of two to four weeks, was considered positive. Later during the outbreak one laboratory used the IFA (Immuno Fluorescence Assay). This latter test distinguished between phases I en II IgM and IgG [13].

Exclusion criteria were: an unknown onset of Q-fever infection, a questionnaire completed by another person or an incomplete questionnaire. Participants younger than 18 years of age, were excluded because the questionnaire instruments were developed for adults.

Questionnaires

All patients that agreed to participate in the Q-Quest I study, received a questionnaire that comprised two parts: the cost and symptoms questionnaire which collected data on demographics, self-reported symptoms, co morbidity, hospitalisation, healthcare consumption, education and employment and the Nijmegen Clinical Screening Instrument *(*NCSI) [14] to measure health status.

The NCSI is based on an empirical definition of health status [15], covering physiological functioning, symptoms, functional impairment, and quality of life (Qol) as main domains. In this study we only measured the main domains symptoms, functional impairment and QoL. These main domains are subdivided into 8 sub-domains: subjective symptoms; dyspnoea emotions; fatigue; behavioural impairment; subjective impairment; general Quality of Life (General QoL); Health Related Quality of Life (HRQoL); and satisfaction with relations [14]. Consult table 1. for definitions and instruments [15-20] of the sub-domains of health status measured by the NCSI.

The NCSI provides normative data indicating normal functioning, mild- or severe problems for each sub-domain. The NCSI contains 8 sub-domains, each expressed as a single score on its own scale. Thus eight different scales were used. The score range indicating severe problems was based on patients with COPD attending a multidisciplinary inpatient pulmonary rehabilitation program (n = 128). The key requirement for inclusion was severe problems in multiple areas of the health status. This decision was based on a three-day intake procedure, in which elaborate assessment, physiological tests and clinical interviews with seven medical disciplines were undertaken. The score range indicating normal functioning was based on a group of healthy subjects (n = 65). Scores below the 80th percentile of healthy controls indicate the score range of normal functioning. Scores above the 20th percentile of the pulmonary rehabilitation group indicate the score range of severe problems. Higher NCSI scores indicate more problems. For more details see Peters *et al* [14].

Table 1. Definitions and instruments of the health status sub-domains measured by the Nijmegen Clinical Screening Instrument

Domain	Sub-domain	Definition	Instruments
Symptoms	Subjective symptoms	The patient's overall burden of pulmonary symptoms	PARS-D Global Dyspnoea Activity, Global Dyspnoea Burden (15)
	Dyspnoea emotions	The level of frustration and anxiety a person experiences when dyspnoeic	DEQ Frustration, Anxiety (15)
	Fatigue	The level of experienced fatigue	CIS Subjective fatigue (16)
Functional impairment	Behavioural impairment	The extent to which a person cannot perform specific and concrete activities as a result of having the disease	SIP Home Management, Ambulation (17)
	Subjective impairment	The experienced degree of impairment in general and in social functioning	QoLRiQ General Activities(18)
Quality of Life	General Quality of Life	Mood and the satisfaction of a person with his/her life as a whole	BDI Primary Care (19) Satisfaction with Life Scale (20)
	Health-related Quality of Life	Satisfaction related to physiological functioning and the future	Satisfaction Physiological Functioning, Satisfaction Future (15)
	Satisfaction relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction spouse, Satisfaction social (15)

PARS-D: Physical Activity Rating Scale-Dyspnoea; DEQ: Dyspnoea Emotions Questionnaire; CIS: Checklist Individual Strength; SIP: Sickness Impact Profile; QoLRiQ: Quality of Life for Respiratory Illness Questionnaire; BDI: Beck Depression Inventory.

Data collection

In February 2009, 870 patients received a Q-Quest study information folder and a participation request form by post. Patients could state their willingness to take part in any of the Q-Quest I studies by signing the consent-form. All patients from the 2007 cohort received a Q-Quest I questionnaire (12-26 months after onset of Q-fever illness) together with the consent form in February 2009. Patients from the 2008 cohort, who had stated their willingness to participate, were mailed the questionnaire exactly one year after the month of onset of illness. If questionnaires were not returned within three weeks, patients from both cohorts received two reminders three weeks apart. See figure 1 for detailed information.

The study design and protocol were approved by the local Medical Ethics Review Committee of the Jeroen Bosch Hospital.

Data analysis

In this study we compared the Q-fever patients NCSI scores with those of the norm groups: healthy individuals (n = 65) and the special group of severe COPD patients (n = 128).

Questionnaires were double scanned in November 2009. SPSS 15.0 for windows was used for statistical analysis. P-values were based on two tailed tests with $p < 0.05$ defined as significant. Chi-square test was used to compare proportions. Logistic regression and the general linear model were used to model outcomes (8 sub-domains of NCSI) for the three groups (healthy COPD-norm group and Q-fever patients), while controlling for the potential confounders: age, gender, smoking and education-level. During logistic regression we regrouped the outcomes normal, mild and severe for the 8 sub-domains into normal and abnormal (combining mild and severe). Notification data of the Municipal Health Service enabled us to compare Q-fever respondents and non-responders for year of onset of illness, age, gender and hospitalisation at the acute stage of the infection. As the control groups providing the normative data for the NCSI were older than 50 years, Q-fever patients younger than 50 years of age were analysed separately from patients older than 50 years.

For comparison of participating Q-fever patients younger or older than 50 years of age, we also looked at co-morbidity and hospitalisation. These data were unavailable for healthy individuals and COPD patients.

RESULTS

Patient participation

Of the 898 patients notified in 2007-2008, 28 were excluded due to incomplete data or unknown month of onset of illness (Figure 1). Of the 5 patients that died, we lacked information on the cause of death. In total 572 questionnaires were received (65.7%). Fewer men than

women returned the questionnaire (responders vs. non-responders women 223/106, men 323/218 p = 0.017). The response rate was higher for patients aged over 35 (*P* = 0.011). After excluding participants younger than 18 years (n = 9), participants who did not complete the questionnaire themselves (n = 22) and incomplete questionnaires (n = 26), 515 questionnaires were left (see Figure 1). The mean interval between the first day of illness for Q-fever patients of cohort 2007 and cohort 2008 and filling out the questionnaire was 19.6 months (SD 2.3) and 11.6 months (SD 1.0), respectively.

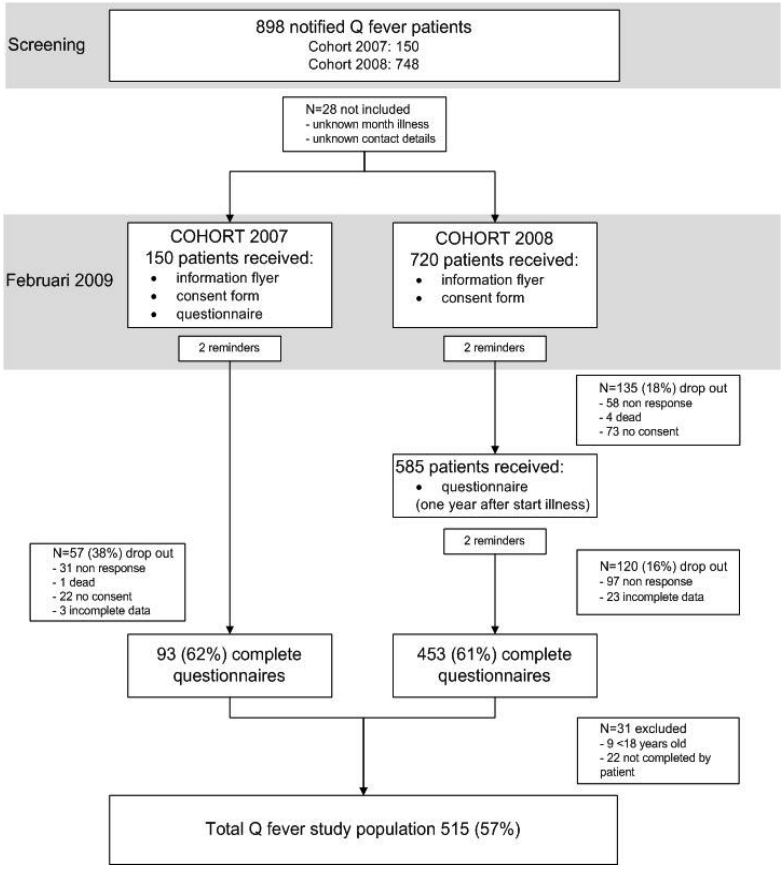

Figure 1. Flowchart. Response rate of 898 Q-fever patients with onset of disease in 2007 and 2008

Characteristics of the study population

Q-fever patients, the healthy and COPD norm group were similar with respect to gender and level of education. The characteristics of the study population are presented in table 2.

Table 2. Characteristics of the study population

	Q-fever				COPD		Healthy		Total
	Age <50		>50 yrs						
Characteristics	**n = 238**	***(%)***	**n = 277**	***(%)***	**n = 128**	***(%)***	**n = 65**	***(%)***	**n = 708**
Gender									
Male	140	*(58.8)*	166	*(59.9)*	86	*(67.2)*	47	*(72.3)*	439
Female	98	*(41.2)*	111	*(40.1)*	42	*(32.8)*	18	*(27.7)*	269
Age									
Mean	40.4		60.3		62.5		63.5		56.7
SD	7.4		7.6		6.9		6.6		
Current smoking									
Yes	96	*(40.3)*	71	*(26.6)*	11	*(8.9)*	11	*(16.9)*	189
No	137	*(57.6)*	196	*(73.4)*	113	*(91.1)*	54	*(83.1)*	500
Education-level									
Low	56	*(23.5)*	97	*(35.5)*	62	*(50.4)*	20	*(30.8)*	235
Average	120	*(50.4)*	126	*(46.2)*	38	*(30.9)*	26	*(40.0)*	310
High	60	*(25.2)*	50	*(18.3)*	23	*(18.7)*	19	*(29.2)*	152

Q-fever patients younger and older than 50 years, Norm groups Chronic Obstructive Pulmonary Disease- and healthy individuals. Q-fever patients >50 currently smoke significantly more than COPD-controls. None of the other characteristics differ significantly (logistic regression).

Health status

The long-term health status of Q-fever patients was severely affected especially for the sub-domains General QoL (44.9%) and fatigue (43.5%) (see figure 2). Almost two fifths of the Q-fever patients (38.2%) older than 50 years, had severe problems on more than one sub-domain (see figure 3). Of the Q-fever patients with abnormal fatigue, 79.5% also reported abnormal scores on subjective symptoms, 77.9% on behavioural impairment, 65.0% on HRQoL, 60.7% on dyspnoea emotions and 57.7% on General QoL.

Female Q-fever patients consistently reported abnormal functioning (mild and severe on the sub-domains of the NCSI) more frequently than males. This difference was only significant for satisfaction with relations (34.0% of the women vs. 28.1% of the men, p = 0.012).

No significant differences were found for 7 sub-domain scores between Q-fever patients older and younger than 50 years. Although the frequency with which dyspnoea was reported was similar for the age groups (45.8% >50 years n = 277 and 42.9% < 50 years n = 238) patients younger than 50 years suffered more often from dyspnoea emotions (OR 2.0, CI 1.3-3.1 p = 0.001).

In comparison to the healthy norm score, Q-fever patients showed significantly more abnormal health status (mild and severe) in 7 of the 8 sub-domains (see table 3). The worst scores were found for the sub-domains fatigue, subjective symptoms and subjective impair-

ment. Q-fever patients had significantly lower (healthier) scores in all 8 NCSI-sub-domains, compared to the COPD-norm score.

The year of onset of illness, level of education and smoking behaviour had no significant influence on sub-domain mean scores. However, patients that were hospitalised (23.6% of patients older than 50 years) during the onset of illness or with underlying heart or lung disease, arthritis and depression scored significantly worse for several sub-domains (see Table 4). The outcomes for patients younger than 50 years were similar.

Heart disease increased the risk for an abnormal outcome for the sub-domains subjective symptoms, behavioural and subjective impairment, HRQoL and dyspnoea emotions. Lung disease had a negative influence on the outcome of the first three aforementioned domains.

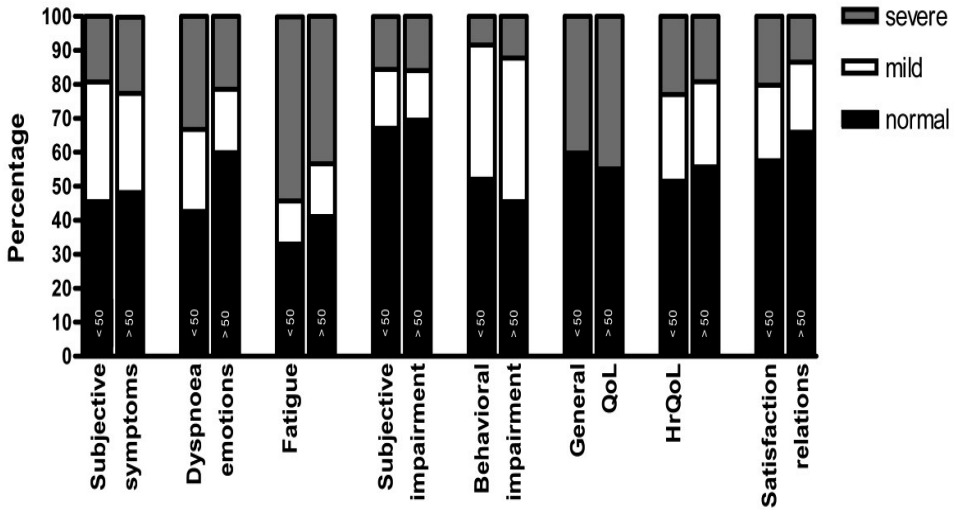

Figure 2. The 8 sub-domain scores of Q-fever patients older (n = 277) and younger than 50 years of age (n = 238).

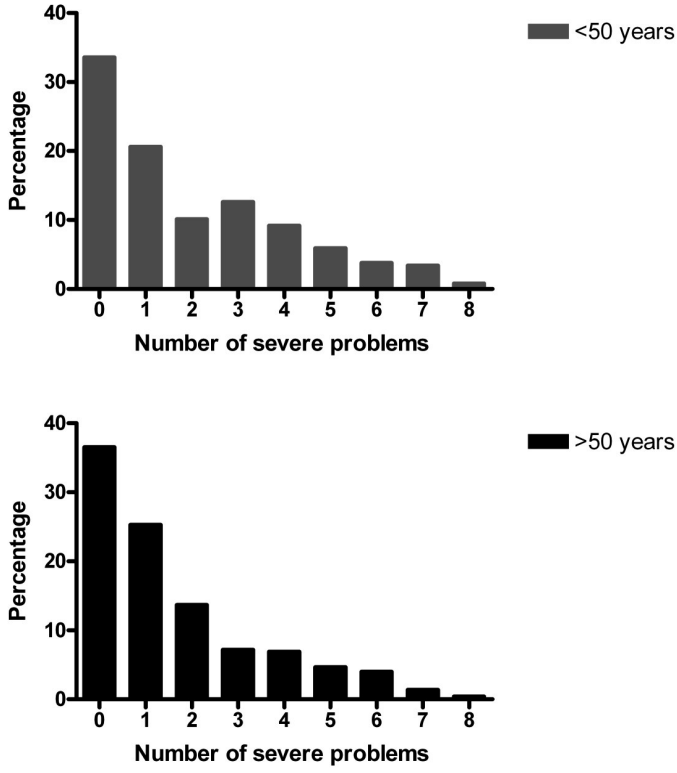

Figure 3. Percentage of Q-fever patients with the number of severely affected domains of the health status.

Table 3. Comparison 8 NCSI sub-domains scores between Q-fever patients > 50 years and the healthy norm group

	Q-fever	Healthy control	Q-fever vs. Healthy (ref)	
Domain and subdomain	**n = 277 (%)**	**n = 65 (%)**	**OR (CI)**	***p*-value**
Symptoms				
Subjective symptoms				
n	255	65		
Normal	123 *(48.2)*	59 *(90.8)*		
Abnormal	132 *(51.8)*	6 *(9.2)*	9.9 (4.0-24.5)	0.000
Dyspnoea emotions				
n	172	65		
Normal	103 *(59.9)*	55 *(84.6)*		
Abnormal	69 *(40.1)*	10 *(15.4)*	3.1 (1.4-6.8)	0.006
Fatigue				
n	207	65		
Normal	85 *(41.1)*	57 *(87.7)*		
Abnormal	122 *(58.9)*	8 *(12.3)*	9.2 (4.0-20.8)	0.000
Functional impairment				
Behavioural impairment				
n	277	65		
Normal	126 *(45.5)*	49 *(75.4)*		
Abnormal	151 *(54.5)*	16 *(24.6)*	3.8 (1.9-7.3)	0.000
Subjective impairment				
n	249	65		
Normal	173 *(69.5)*	60 *(92.3)*		
Abnormal	76 *(30.5)*	5 *(7.7)*	5.0 (1.9-13.4)	0.001
Quality of life				
General Quality of Life				
n	234	65		
Normal	129 *(55.1)*	51 *(78.5)*		
Abnormal	105 *(44.9)*	14 *(21.5)*	2.4 (1.2-4.7)	0.011
Health related Quality of Life				
n	271	65		
Normal	151 *(55.7)*	55 *(84.6)*		
Abnormal	120 *(44.3)*	10 *(15.4)*	3.7 (1.8-7.7)	0.001
Satisfaction relations				
n	252	65		
Normal	166 *(65.9)*	37 *(56.9)*		
Abnormal	86 *(34.1)*	28 *(43.1)*	0.5 (0.3-0.9)	0.040

Abnormal is a combination of mild and severe scores. Used method chi square.

Table 4. Probability of long-term impaired health-status amongst Q-fever patients older than 50 years (n = 277)

Domain	**Symptoms**												**Functional impairment**			
Sub-domain	**Subjective symptoms n = 247**				**Dyspnoea emotions n = 166**				**Fatigue n = 201**				**Behavioural impairment n = 269**			
Factor	**n**	**OR**	**(95% CI)**	***p*-value**	**n**	**OR**	**(95% CI)**	***p*-value**	**n**	**OR**	**(95% CI)**	***p*-value**	**n**	**OR**	**(95% CI)**	***p*-value**
Hospitalised	58	1.9	(1.1- 3.6)	0.026	40	1.9	(0.9- 3.8)	0.080	41	1.7	(0.8- 3.4)	0.154	62	2.8	(1.5- 5.1)	0.001
Diabetes	21	1.1	(0.4- 2.6)	0.895	16	0.9	(0.3- 2.7)	0.902	16	1.7	(0.6- 4.9)	0.365	25	2.4	(0.9- 5.9)	0.062
Heart disease	32	2.3	(1.1- 5.2)	0.035	17	3.3	(1.1- 9.3)	0.027	22	1.6	(0.6- 4.2)	0.305	34	3.2	(1.4- 7.3)	0.007
Lung disease	17	5.3	(1.5-18.7)	0.010	10	2.9	(0.8-10.3)	0.100	12	4.3	(0.9-19.8)	0.064	18	4.9	(1.4-17.5)	0.012
Arthritis	10	9.2	(1.2-73.9)	0.036	5	2.4	(0.4-14.9)	0.341	7	4.5	(0.5-38.4)	0.165	12	4.5	(0.9-21.0)	0.054
Depression	10	2.3	(0.6- 9.2)	0.232	5	6.6	(0.7-60.6)	0.094	9	1.5	(0.4- 6.1)	0.589	10	3.6	(0.7-17.1)	0.112
Domain	**Functional impairment**				**Quality of Life (QoL)**											
Sub-domain	**Subjective impairment n = 241**				**General QoL n = 234**				**Health related QoL n = 263**				**Satisfaction relations n = 245**			
Factor	**N**	**OR**	**(95% CI)**	**p**	**N**	**OR**	**(95% CI)**	***p*-value**	**N**	**OR**	**(95% CI)**	***p*-value**	**N**	**OR**	**(95% CI)**	***p*-value**
Hospitalised	52	1.4	(0.7- 2.7)	0.274	47	0.9	(0.5- 1.8)	0.894	47	2.3	(1.3-4.0)	0.005	56	1.3	(0.7- 2.4)	0.343
Diabetes	23	1.3	(0.5- 3.2)	0.570	18	0.6	(0.2- 1.6)	0.298	18	1.2	(0.5-2.8)	0.626	24	0.8	(0.3- 2.0)	0.649
Heart disease	30	2.7	(1.2- 5.9)	0.011	25	1.4	(0.6- 3.1)	0.469	25	2.6	(1.2-5.5)	0.014	33	1.8	(0.4- 1.9)	0.692
Lung disease	16	13.3	(3.7-47.9)	0.000	13	0.9	(0.3- 2.7)	0.869	13	2.1	(0.8-5.7)	0.128	15	2.1	(0.7- 5.8)	0.159
Arthritis	11	12.1	(2.5-57.4)	0.002	7	1.6	(0.4- 7.5)	0.522	7	7.0	(1.5-32.8)	0.013	11	1.1	(0.3- 4.0)	0.827
Depression	9	1.9	(0.5- 7.5)	0.329	8	9.0	(1.1-74.7)	0.041	8	3.1	(0.8-12.6)	0.100	10	8.7	(1.8-42.2)	0.007

Logistic regression modelling. In all determinants “no” was the reference. Smoking and education-level were not included due to overall insignificant results.

DISCUSSION

The present study is the largest and longest follow-up study of Dutch Q-fever patients of the 2007 and 2008 outbreaks. Using a validated questionnaire, the Nijmegen Clinical Screening Instrument (NCSI), we provided a detailed assessment of the long-term effects of Q-fever on health status 12-26 months after onset of illness. The most important finding of this study was that, in two thirds of Q-fever patients of all ages, at least one sub-domain was severely (clinically) affected up to 26 months after the initial illness. The sub-domains General QoL (44.9%) and fatigue (43.5%) were most frequently severely affected.

Published data on health status, and its sub-domains, in Q-fever patients are scarce. Hatchette reported [21] that 52% of Q-fever patients were symptomatic and had an impaired QoL 27 months after infection, with significant lower scores on five of eight domains of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), as compared to non-infected controls. Impaired domains were: physical pain, physical function, emotional role, physical role and social function.

In our study we found 58.9% of patients with abnormal (mild and severe) fatigue. This is similar to other publications that state 68.7% [9] five and 64.9% [8] protracted fatigue up to ten to years after infection. Unfortunately we were unable to establish if Q fever patients mainly suffered fatigue the first year and later recovered as we only had contact with patients once. The fact that we found no differences between patients of the 2007 and 2008 cohorts is suggestive of persisting complaints.

Some studies state that cytokine deregulation and immuno-modulation from persistence of *C. burnetii*, might be responsible [22] for prolonged fatigue, but others contradict this [23].

Other studies find prolonged impairment of the health status months after legionellosis and pneumonia. Dutch pneumonia patients had significantly affected SF-36 scores 18 months after pneumonia on the subscales physical function and general health status [24]. Survivors of a Legionnaires Disease-outbreak in the Netherlands reported 17 months after infection severely impaired SF-36-domains: physical role function, general health and vitality [25]. Up to 75.0% of patients reported fatigue [25]. Although all three infectious diseases seem to cause long-term impairment; the impaired sub-domains differ.

The severity of initial illness in general negatively influences the long-term QoL [26, 27]. Similarly, the severity of the acute Q-fever symptoms predicts long-term symptoms [28]. Our study shows that hospitalised patients more often scored abnormal on the sub-domains HRQoL, behavioural impairment and subjective symptoms than those that were not hospitalised during the acute phase of illness. We consider hospitalisation to be an indicator of the severity of the initial infection. Our assumption that Q-fever patients with severe acute illness are more likely to experience long-term impaired QoL was therefore proven correct.

Another study shows that patients that had been admitted to the Intensive Care Unit- regardless of the cause- have an impaired QoL (SF-36) up to 18 months [29].

General QoL (44.9%) and fatigue (43.5%) were severely affected in our study subjects. A small study on Dutch Q-fever patients that measured the one year follow-up and also used the NCSI reported a higher rate of 53% of patients with severe fatigue [12]. We suspect that the patients in that study had a higher hospitalisation rate and presented with more pneumonia than our patients. Consultation of our notification data confirmed this presumption, but the difference was marginal. Furthermore, proportionally more patients in that study might have been recruited from the local hospital's chest clinic. In the present study, we approached all patients in the region, regardless of the severity of the initial disease.

We found that heart disease increased the risk of subjective symptoms, behavioural and subjective impairment, HR QoL and dyspnoea emotions. Whereas lung disease negatively influenced the outcomes of the first three of these sub-domains.

Other authors stated that underlying heart [30,31] or lung disease [32], arthritis [33], depression [34] and diabetes [35], all had a negative effect on the health status in different sub-domains. We also found this effect, except for diabetes, but could not compare data with existing studies, as most of these studies focus on specific diseases (such as COPD) and grades of severity. We however, combined all diseases of a certain tract.

Methodological considerations and study limitations

The NCSI is not widely used in Q-fever research. This makes comparison to other QoL-research in Q-fever difficult. The advantage of the NCSI is that it provides a detailed assessment including many domains of health status covering symptoms, functional impairment and quality of life. The NCSI provides more and specific information on sub-domains than some of the other instruments such as the SF-36. Furthermore, the availability of datasets of both a COPD and a healthy norm group for the NCSI, enabled us to compare the health status of Q-fever patients with these two groups. Such a comparison provides useful information for GPs and medical specialists in their understanding of Q-fever patients. Another advantage is that the NCSI questionnaire for the domain fatigue is based on the CIS (Checklist Individual Strength). This instrument corrects for normal fatigue [36]. As many Q-fever patients suffer from fatigue, the NCSI seemed the right choice.

The municipal health service regularly received Q-fever patient reports of continuing respiratory complaints. We therefore looked for a norm group with a known respiratory component that we could compare these Q-fever patients with. When we compared data from Q-fever patients with the NCSI norm group of COPD patients it should be realized that this is a specific subgroup of COPD patients with a severely impaired health status in multiple sub-domains. We made the choice to use this COPD norm group as we wished to compare

the long-term health status of Q-fever patients (who often suffered a pneumonia initially) with another group of patients with a known impaired health status.

The healthy control group was rather small with 65 individuals all over 50 years of age. However, the number of controls provided sufficient power for us to show a large and clear difference between the groups.

Normative data of healthy subjects and those with COPD were only available for patients older than 50 years of age. This was unfortunate as 46.2% of Q-fever patients were younger than 50. As we chose our method to be as strict and transparent as possible, we presented data for patients younger and older than 50 years of age separately.

In at least 1.6% of the Q-fever patients in the Dutch 2007-2008 cohorts, the condition became chronic (van der Hoek *et al*, submitted for publication). For our study population this could potentially mean eight or nine patients with chronic Q-fever. As not all patients in our study were followed up serologically we were unable to establish if and who developed chronic Q-fever or any of its presentations such as endocarditis.

Data were collected during the early stages of the Q-fever outbreaks in the Netherlands. At that stage there was little to no media attention for these outbreaks. The general public was mostly unaware of Q-fever and the possible negative long-term outcome. Patients were not medicalised and mostly unaware. We therefore believe that our data were not negatively influenced by the media or the general knowledge of the patient of the negative long-term outcomes.

Implications

By assessing the long-term health status of Q-fever patients of the largest outbreak in the world, we are able to describe and quantify the impact of Q-fever on patient's lives. Hospitalisation is an important predictor of severe illness, poor long-term health status outcome and long-term absence from work (unpublished data G.Morroy).

The outbreaks are continuing and Q-fever has become endemic in the area. Since symptoms could last for ten years or more [8], the burden of disease for the affected communities is likely to be considerable.

A better understanding of long-term outcomes is essential for policy makers dealing with these outbreaks. GPs and other Medical Doctors should be aware that Q-fever patients may present with long-term symptoms especially in those that were hospitalised and or with co-morbidity (heart-, lung-disease, and depression). Knowledge of these detrimental long-term outcomes should help MDs to be more supportive to these patients and refer promptly and adequately to specialist care.

Conclusions

Our study of the largest described Q-fever cohort in the world shows a large long-term impact of Q-fever on the health status of Q-fever patients of all ages. This is but an indication of the burden of disease in the years to come considering the more than 4,000 reported Dutch Q-fever cases since 2007. Policy makers ought to take the long-term burden of disease into account, when considering measures to be taken to curb these extensive Dutch outbreaks. We recommend further research to develop adequate prevention, treatment and revalidation guidelines that might benefit these affected patients.

ACKNOWLEDGEMENTS

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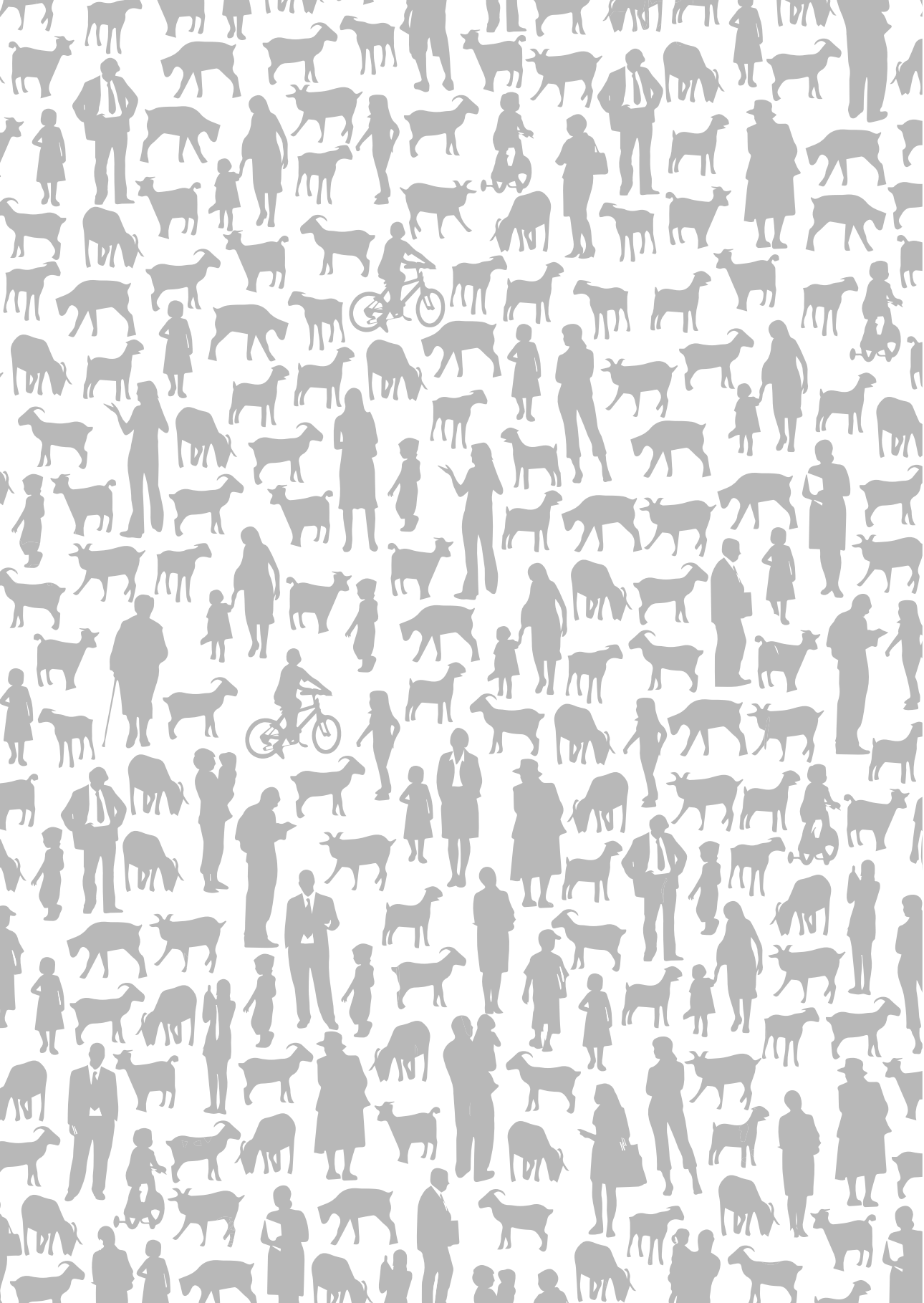

Chapter 8

THE HEALTH STATUS OF A VILLAGE POPULATION, SEVEN YEARS AFTER A MAJOR Q-FEVER OUTBREAK

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SUMMARY

From 2007 through 2010, the Netherlands experienced a major Q-fever outbreak with more than 4000 notifications. Previous studies suggested that Q-fever patients could suffer long-term post infection health impairments, especially fatigue. Our objective was to assess the *Coxiella burnetii* antibody prevalence and health status including fatigue, and assess their interrelationship, in Herpen a high incidence village, seven years after the outbreak began.

In 2014, we invited all 2161 adult inhabitants for a questionnaire and a *C. burnetii* Indirect Fluorescence Antibody Assay (IFA). The health status was measured with the Nijmegen Clinical Screening Instrument (NCSI), consisting of eight sub-domains including fatigue.

Of the 70.1% (1517/2161) participants, 33.8% (513/1517) were IFA positive. Of 147 participants who were IFA positive in 2007, 25 (17%) seroreverted and were now IFA negative. Not a positive IFA status, but an age <50 years, smoking and co-morbidity, were independent risk factors for fatigue. Notified participants reported significantly more often fatigue (31/49, 63%) than not notified IFA positive participants (150/451, 33%). Although fatigue is a common sequel after acute Q-fever, we found -in this community-based survey- no difference in fatigue levels between participants with and without *C. burnetii* antibodies.

INTRODUCTION

Q-fever is a zoonosis caused by the bacterium *Coxiella burnetii (C. burnetii)*. In 2007, Herpen, a small village in the south of the Netherlands was heavily affected by a Q-fever outbreak [1]. This outbreak was followed by larger outbreaks in 2008 and 2009, in a larger geographical area and culminated in 4107 notifications nationwide by 2010 [2].

A common sequel of acute Q-fever is protracted incapacitating fatigue [3-5], often denoted as the Q-fever Fatigue Syndrome (QFS) that may continue ten years or longer[6,7]. Patients with QFS may experience severe sweating, breathlessness, blurred vision, reduced exertion, myalgia, arthralgia, sleeping disorders and mood swings [7, 8], symptoms that resemble the Chronic Fatigue Syndrome (CFS). The aetiology of QFS is not entirely understood. Dysregulation of cytokines due to persisting antigens of *C. burnetii* are described to cause chronic stimulation of the immune system [9, 10]. A Post Infection Fatigue Syndrome (PIFS) [11] may also occur after other infections [12], such as *Borrelia burgdorferi* [13], *Legionella pneumophila* [14], *Epstein Barr* and *Ross River virus* infection [12]. According to several studies, Q-fever patients have an impaired health status, pulmonary disorders and an increased risk of problems in general and social functioning [3-8, 12, 14].

General practitioners (GPs) and the population in the Q-fever affected area, and the national Q-fever patient organisation, speculated that the number of infections and long-term consequences such as fatigue were underestimated. The local municipal health service (MHS) therefore initiated the 'Q-Herpen-II' study in- this small rural village with a stable Caucasian population – in order to investigate the presence of antibodies against *C. burnetii* in relation to the health status with an emphasis on fatigue.

METHODS

Study design and study population

The Municipal Health Service (MHS) "GGD Hart voor Brabant" executed this study as part of the larger 'Q-Herpen-II' study. The Medical Ethics Review Committee of the Utrecht University Medical Centre, approved the study (protocol 13-367/D Q-Herpen II). For this cross-sectional population study all adult inhabitants (≥18 years of age) of the village Herpen (postal code 5373) were invited to participate. The municipal administration provided demographic data for the 2161 inhabitants. In January 2014, all were sent a letter by mail containing information on the study with a participation request, a questionnaire and an informed consent form. The questionnaire included questions on demographics, smoking, the participant's knowledge or perception of their Q-fever status, risk factors associated with chronic Q-fever, Q-fever vaccination status, chronic medical conditions and medication use.

Table 1. Domains and sub-domains of the Nijmegen Clinical Screening Instrument (NCSI) with their definition, the instruments on which they are based and number of question used.

Domains	Sub-domain	Definition	Instruments	Number of questions
Symptoms	Subjective Pulmonary Symptoms	Overall burden of pulmonary symptoms	PARS-D[1] Global Dyspnoea Activity, Global Dyspnoea Burden	2
	Dyspnoea Emotions	Level of frustration and anxiety experienced when dyspnoeic	DEQ[2] Frustration, Anxiety	6
	Fatigue	Level of experienced fatigue	CIS[3] Subjective Fatigue	8
Functional Impairment	Behavioural Impairment	The extent of inability to perform specific and concrete activities as a result of the disease	SIP[4] Home Management, Ambulation	22
	Subjective Impairment	Experienced degree of impairment in general and in social functioning	QoLRiQ[5] General Activities	4
Quality of Life	General (GQOL)	Mood and the satisfaction with life as a whole	BDI[6] Primary Care Satisfaction With Life Scale	12
	Health Related (HRQOL)	Satisfaction related to physiological functioning and the future	Satisfaction Physiological Functioning, Satisfaction Future	2
	Satisfaction Relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction Spouse, Satisfaction Social	2

PARS-D[1] physical activity rating scale-dyspnoea, *DEQ*[2] dyspnoea emotions questionnaire, *CIS*[3] checklist individual strength, *SIP*[4] sickness impact profile, *QoL-RiQ*[5] quality of life for respiratory illness questionnaire, *BDI*[6] beck depression inventory.

The current health status was assessed with the Nijmegen Clinical Screening Instrument (NCSI), which is a validated method originally developed to measure the health status of COPD patients in a clinical setting [15]. The instrument consists of the main domains: Symptoms, Functional Impairment, and Quality of Life. These are divided into eight sub-domains (table 1). Patients' scores are subdivided in "normal", "mild problems" and "clinically relevant problems". The only exception is the sub-domain General Quality of Life that is divided in "normal" and "clinically relevant problems"/"severe problems". In the univariate and multivariate analysis, the NCSI categories mild problems and clinically relevant problems were

combined into one category problems. Age, smoking behaviour, and educational level were dichotomized.

During five days in February and one in March 2014, questionnaires were handed in by participants and checked for missing information and errors by medical staff together with the participant. This was followed by a venipuncture.

Antibodies against *C. burnetii* were determined with the Indirect Fluorescence Antibody Assay (IFA). An IFA IgG phase I or II titre ≥1:64 was considered positive. The IFA results were reported to participants and their GPs with a medical recommendation. Data on the occurrence of chronic Q-fever are described in a separate publication [16].

We verified if participants had been notified previously, by using the local MHS data. In the Netherlands acute Q-fever is notifiable. Any acute Q-fever diagnosis must be reported to the MHS both by the clinician and the laboratory of medical microbiology. Reported cases that according to the MHS meet the predefined national case definitions are notified and registered in a national surveillance system. Notification criteria used at the beginning of the outbreak in 2007 were: a laboratory confirmation and matching clinical symptoms. In July 2008 the Dutch Q-fever notification criteria were changed to; the presence of fever, pneumonia or hepatitis and a laboratory diagnosis plus reported to the MHS within 90 days following the onset of illness. For notification at least one of the following laboratory criteria should be met: seroconversion or a fourfold or larger *C. burnetii* IgG-antibody titre increase in paired sera (minimally two weeks apart) of an IFA or a complement fixation test (CFT), or presence of IgM-Phase II antibodies or a positive *C. burnetii* PCR (unless the sample is from a patient with chronic Q-fever). If any of the clinical, laboratory or time criteria were not met a Q-fever case would-although reported- not be registered (notified) in the national surveillance system.

We assumed that IFA positive (IgG phase I or II ≥ 1:64) participants who reported that they did not to recall an acute Q-fever episode, had either previously experienced an asymptomatic or mild acute infection, which had not been medically evaluated. These individuals were classified as “no recollection of a previous infection”. Participants that were adamant that they had been infected and reported their belief in a past infection even if this was regardless of any medical proof were classified as “belief in a previous infection”. We conducted a stratified analysis- the Mantel Haenzel Summary Chi Square test-to control for the confounding effect of knowledge of/belief in a past episode of acute Q-fever. It is therefore not a multivariate statistical model.

Statistical analysis

Questionnaires were digitally scanned into a SPSS database and analysed with SPSS 21.0 and Open Epi. Information on age and gender of non-participants was obtained from the municipal administration.

Participants that had been vaccinated against Q-fever were excluded from the analysis.

Proportions were compared with the chi-square test. Multivariate logistic regression analyses was used to compare the NCSI sub-domain scores incorporating the 2014 IFA status, age, gender, smoking, educational-level, rheumatoid arthritis, psychiatric disorders and or use of psychiatric medication, and other co-morbidity. A *p*-value <0.05 was considered significant.

RESULTS

Participants and non-participants

Of the 2161 inhabitants, 70.9% (1534/2161) participated. Both a blood sample and a questionnaire were received from 70.2% (1517/2161) participants.

Participants and non-participants were comparable with respect to gender and age (data not shown).

Characteristics and IFA status of participants

Of the participants 33.8% (n=513) were IFA positive. As the five participants vaccinated against Q-fever were removed from our database, data were analysed for the remaining 1512 participants, including 510 IFA positives.

There were no differences in gender, age, educational level and presence of co- morbidity between IFA positive and IFA negative participants (Table 2). IFA positive participants were more often current smokers than IFA negative participants (Table 2). Of note; of the 147 participants who were IFA positive in 2007, 25 (17%) seroreverted and were IFA negative in 2014 [16].

NCSI sub-domains in relation to IFA status

IFA positive participants did not score significantly higher (worse) on NSCI sub-domains compared to IFA negative participants (Figure 1, for data see supplementary Table S1). On the contrary, amongst IFA positive participants, the ORs for the three sub-domains; subjective pulmonary complaints (OR 0.69 (CI 0.55-0.88), $p<0.01$), dyspnoea emotions (OR 0.65 (CI 0.49-0.85), $p<0.01$) and subjective impairment (OR 0.77, (CI 0.59-0.98), $p=0.04$) were <1.

Table 2. Characteristics of study participants and the presence of *Coxiella burnetii* antibodies measured with the immunofluorescence assay (IFA).

	All		IFA-positive		IFA-negative		
	n=1512	***100%***	**n=510**	***(33.8%)***	**n=1002**	***(66.2%)***	***p*-value**
Mean age, years	51.9	(SD 16.5)	51.5	(SD 15.7)	52.1	(SD 16.9)	0.54[1]
Gender							0.70[2]
Male	748	*(49.6)*	256	*(50.2)*	492	*(49.1)*	
Female	764	*(50.4)*	254	*(49.8)*	510	*(50.9)*	
Smoking							0.04[2]
Current	276	*(18.3)*	110	*(21.6)*	166	*(16.6)*	
Former	565	*(37.5)*	191	*(37.5)*	374	*(37.5)*	
Never	666	*(44.2)*	209	*(41.0)*	457	*(45.8)*	
Educational level[2]							0.05[2*]
Low	822	*(55.2)*	289	*(57.5)*	533	*(54.0)*	
Average	425	*(28.5)*	149	*(29.6)*	276	*(28.0)*	
High	243	*(16.3)*	65	*(12.9)*	178	*(18.0)*	
Known or perceived previous Q-fever [2]							
Yes, medically confirmed	147	*(9.8)*	122	*(24.1)*	25	*(2.5)*	<0.01[2]
Yes, own belief	46	*(3.1)*	23	*(4.5)*	23	*(2.3)*	
No	775	*(51.8)*	219	*(42.3)*	556	*(56.2)*	
Don't know	527	*(35.3)*	142	*(28.1)*	385	*(38.9)*	
Rheumatoid arthritis							
Yes	127	*(8.4)*	37	*(7.3)*	90	*(9.0)*	0.28[2]
No	1378	*(91.6)*	471	*(92.7)*	907	*(91.0)*	
Psychological disease or medication[2]							
Yes	80	*(5.3)*	31	*(6.1)*	49	*(4.9)*	0.33[2]
No	1430	*(94.7)*	479	*(93.9)*	951	*(95.1)*	
Other co-morbidity							
Yes	442	*(29.3)*	144	*(28.2)*	298	*(29.8)*	0.55[2]
No	1069	*(70.7)*	366	*(71.8)*	703	*(70.2)*	

[1]Analysed with the independent sample *t*-test or [2]the Pearson's chi-squared test. * The actual *p*-value is 0.054.

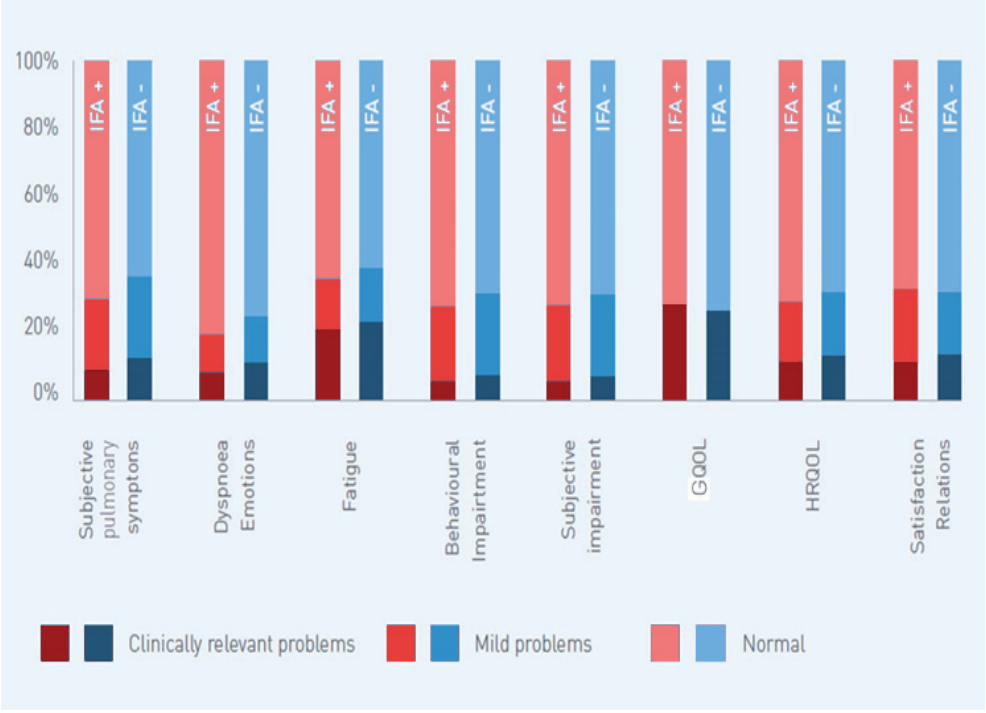

Figure 1.NCSI sub-domains in paired columns as IFA positive (IFA+) (n= 509) and negative (IFA-) (n= 998) divided in: clinically relevant problems bottom, mild problems –middle and normal top.
GQOL is General Quality of Life and HRQOL is the Health Related Quality of Life.

A positive IFA status was not an independent risk factors for fatigue in the multivariate model but being younger than 50 years of age, a current smoker, and having an underlying medical condition (co-morbidity) were Table 3. See Table 4. for the independent risk factors for the general quality of life (GQOL).

Regardless of the IFA status 37.7% of participants reported fatigue including 22.6% with clinically relevant fatigue. Participants with chronic medical conditions such as psychiatric disorders had both a severely impaired GQOL and fatigue in resp. 64.0% and 48.0% of cases. While 35.4% of participants with rheumatoid arthritis had a severely impaired GQOL, for fatigue this was 36.9%.

When using the IFA titre as a semi-quantitative measure, participants with a higher IFA titre did not report more fatigue than those with a lower IFA titre (data not shown).

Table 3. Univariate and multivariate logistic regression of factors for the outcome fatigue[1].

	Fatigued[1]							
	Univariate analysis				Multivariate analysis			
Characteristic	**Total n**	**OR**	**CI**	***p*-value**	**Total n**	**OR**	**CI**	***p*-value**
IFA								
Positive	482	0.8	(0.7-1.1)	0.2	472	0.8	(0.6-1.03)	0.08
Negative	942	1.0[2]			921	1.0[2]		
Age dichotomous								
≤50	654	1.4	(1.1-1.7)	<0.01	641	2.0	(1.5-2.5)	<0.01
>50	780	1.0[2]			752	1.0[2]		
Gender								
Female	730	1.3	(1.1-1.6)	0.01	705	1.2	(0.9-1.5)	0.12
Male	704	1.0[2]			688	1.0[2]		
Smoking								
Current	260	1.9	(1.5-2.6)	<0.01	256	1.8	(1.3-2.4)	<0.01
Former or never	1172	1.0[2]			1137	1.0[2]		
Education level								
Median and high	756	1.2	(0.9-1.5)	0.05*	751	1.3	(1.0-1.6)	0.05**
Low	642	1.0[2]			642	1.0[2]		
Rheumatoid arthritis								
Yes	122	2.1	(1.4-3.0)	<0.01	122	2.1	(1.4-3.2)	<0.01
No	1309	1.0[2]			1309	1.0[2]		
Psychiatric condition/medication								
Yes	75	4.6	(2.7-7.7)	<0.01	74	4.1	(2.4-6.9)	<0.01
No	1359	1.0[2]			1319	1.0[2]		
Other chronic diseases								
Yes	418	1.9	(1.5-2.4)	<0.01	407	2.0	(1.6-2.6)	<0.01
No	1016	1.0[2]			689	1.0[2]		

[1]Fatigue is divided in normal versus the combination of mild and clinically relevant fatigue scores here called fatigued or abnormal fatigue score. [2] Is the reference group. *The actual p-value is 0.053 and **0.054 respectively.

Table 4. Univariate and multivariate logistic regression of factors for the outcome General Quality of Life (GQOL)[1]

Clinically relevant abnormal General Quality of life[1]								
	Univariate analysis				Multivariate analysis			
Characteristic	**Total n**	**OR**	**CI**	***p*-value**	**Total n**	**OR**	**CI**	***p*-value**
IFA								
Positive	497	1.1	(0.9-1.4)	0.46	487	1.0	(0.8-1.3)	0.94
Negative	978	1.0[2]			954	1.0[2]		
Age dichotomous								
≤50	665	0.9	(0.7-1.1)	0.35	651	1.4	(1.1-1.8)	0.01
>50	825	1.0[2]			790	1.0[2]		
Gender								
Female	752	0.9	(0.7-1.1)	0.27	718	1.0	(0.8-1.3)	0.88
Male	738	1.0[2]			723	1.0[2]		
Smoking								
Current	266	1.5	(1.1-2.0)	<0.01	260	1.3	(0.9-1.8)	0.09
Former or never	1222	1.0[2]			1368	1.0[2]		
Education level								
Median and high	790	1.2	(0.9-1.6)	0.08	785	1.2	(0.9-1.6)	0.14
Low	656	1.0[2]			656	1.0[2]		
Rheumatoid arthritis								
Yes	127	1.5	(>1.0-2.2)	0.38	121	1.5	1.0-2.3)	0.06
No	1359	1.0[2]			1,32	1.0[2]		
Psychiatric condition/medication								
Yes	75	5.2	(3.2-8.4)	<0.01	73	4.7	(2.9-7.8)	<0.01
No	1415	1.0[2]			1368	1.0[2]		
Other chronic diseases								
Yes	441	1.5	(1.2-1.9)	<0.01	424	1.4	(1.1-1.9)	0.04
No	1049	1.0[2]			1017	1.0[2]		

[1]GQOL is divided in normal versus clinically relevant abnormal GQOL. [2]Is the reference group.

Notification in relation to the subdomains fatigue and General Quality of Life

Of the 510 IFA positive participants, 51 had previously been notified for acute Q-fever, 49 of whom completed the sub-domain fatigue part of the questionnaire. These notified participants presented significantly more often mild and clinically relevant fatigue 63.3% (n=31/49), Table 5, than IFA positive participants with a known positive Q-fever status, who had not fitted the notification criteria combined with those who were first identified during this study 33.3% (n=150/451), OR 3.4 (1.9-6.5) p<0.01. These notified and not notified IFA positive participants did not differ significantly for the subdomain General Quality of Life (GQOL).

Table 5. Notification status and characteristics of 500 IFA positive participants in relation to the fatigue status.

	Total	Male				Age ≤50 years		Fatigue status					
								Normal		Mild problem		Clinical relevant problem	
	n	n	%	Mean age	(SD)	n	%	n	(%)	n	(%)	n	(%)
Notified	49	29	*58.2*	52.9	*(14.3)*	22	*44.9*	18	36,7	8	16,3	23	46,9
Positive not notified	72	47	*65.3*	56.3	*(11.7)*	19	*26.4*	49	68,1	6	8,3	17	23,6
Identified in 2014	379	176	*46.4*	50.2	*(16.3)*	187	*49.3*	252	66,5	54	14,2	73	19,3
Total	500							319		68		113	

Belief in a previous Q-fever infection in relation to fatigue

The questionnaire contained several questions about perceived or medically confirmed acute Q-fever. Among the 181 participants that reported a medically confirmed diagnosis or believed that they had suffered from acute Q-fever, 137 (76%) were IFA positive in 2014 (Supplementary Table S2). We assumed that IFA positive participants who did not recall an acute Q-fever episode had previously experienced an asymptomatic acute infection, or mild illness that had not been medically evaluated. A stratified analysis showed no evidence of confounding by belief in a past Q-fever episode in the relationship between IFA status and fatigue (Supplementary Table S2).

DISCUSSION

In this unique and large cross-sectional population study in a Q-fever high incidence village, seven years after a large Q-fever outbreak, we found a high seroprevalence *C. burnetii* of antibodies of 34%. An impaired general quality of life or abnormal fatigue status was not

associated with *C. burnetii* IFA positive serological test results. Overall 37.7% participants reported fatigue including 22.6% with clinically relevant fatigue. In the nearby city of Nijmegen, the Netherlands, a study in 2009 found that more than 30% of a random population sample suffered from fatigue for longer than six months [17]. A German study, also reported that 30% of participants from a general population sample reported moderate fatigue during the last six months whilst 10% of participants had substantial fatigue for the last six months or longer [18]. These two studies clearly indicate that fatigue levels in the general population are high. The reported 37.7% prevalence figure for fatigue in our study seems large, but when compared to the above mentioned figure of 30% is not. As these two studies used different instruments to assess fatigue, only a rough comparison of prevalence of fatigue is possible.

The GQOL and fatigue were in this study severely impaired in participants with chronic medical conditions such as psychiatric disorders and rheumatoid arthritis. The influence of chronic medical conditions on fatigue has been reported previously for psychiatric disorders [19, 20, 21], rheumatoid arthritis [22] diabetes [23], and heart failure [24, 25].

Studies in the Netherlands and elsewhere clearly documented persisting fatigue and an impaired quality of life after Q-fever. These studies focused on proven acute Q-fever episodes, i.e. patients with clinical disease and with a confirmed laboratory diagnosis that often fitted the national notification criteria (symptomatic cases) [3, 4, 11, 14, 26]. Our findings are in line with the international literature, as we also documented persisting fatigue in the small group of 49 previously notified participants. However, in this community-based study we found no increased risk for an impaired health status or fatigue in participants with *C. burnetii* antibodies. Nor could we find a relationship between the fatigue level and IFA titre. This finding was similar to data from Hussain-Yusuf *et al.* [27] who also found no detectable relationship between fatigue levels and serology six years after exposure.

The present study and other studies support the notion that the severity of symptoms during the acute episode predicts long-term symptoms such as fatigue [4, 12] and that QFS follows clinically overt infections, but rarely that of a subclinical infection [28]. While the severity of the infection during the acute phase (here notification) was related to the intensity of the later PIFS, psychological and microbiological factors were not.

The majority of participants with a positive IFA result had never been notified for acute Q-fever, presumably because the acute infection episode had passed with only mild clinical symptoms or was entirely asymptomatic.

A previous study from the Netherlands reported no significant difference in the NCSI sub-domain scores between asymptomatic cases infected with *C. burnetii* (n=11) and healthy controls (n=23) [5]. Although the sample size was small results are in accordance with our findings.

A comparison between patients with a lower respiratory tract infection (LRTI) of several causes (n=32) and those with Q-fever (n=50) showed no significant differences for most NCSI

sub-domains (including fatigue and (GQOL) approximately 15 months after the initial infection [29]. Twelve months after the onset of symptoms 50% vs. 42.6% of patients with a *Legionella* infection had respectively severe fatigue and GQOL (measured with the NCSI) [14]. But notified (and therefore symptomatic) Q-fever patients scored worse for respectively severe fatigue and GQOL with 60.2% and 50.0% compared to those with a *Legionella* infection [14].

We were unable to verify the severity of any acute illness episode with certainty because the acute episode could have taken place years ago. We speculated that participants who believed that they had suffered from an acute Q-fever episode in the past would report current fatigue more often. We also expected to find that people with fatigue in communities affected by Q-fever would attribute their fatigue to a previous Q-fever episode, even when acute Q-fever was not medically diagnosed. However, our analysis showed that this factor was not significant and could be disregarded.

From historical data we know that 17% of participants from this population that were IFA seropositive in 2007, had become seronegative by 2014 [16].This shows that negative Q-fever serology does not rule out a previous *C. burnetii* infection which should be taken into account if high risk populations are vaccinated against Q-fever. This also shows that Q-fever serology is insufficient to diagnose whether long-term fatigue might been caused by Q-fever.

The major strengths of this study are the high response rate of 70.9%, a questionnaire check on the spot and the inclusion of participants from the same homogenous village with a high-Q-fever prevalence. This is the first large study to compare IFA positive and negative cases from the same homogenous population. The whole spectrum from initially asymptomatic, mildly symptomatic and severe symptoms during an acute Q-fever infection is included. Furthermore the control groups used in many other studies, were often healthier than the general population as only individuals without known comorbidities were selected [3, 4, 14]. Our control group included participants with comorbidities and is therefore a realistic representation of the general population. Together this results in unique and robust data.

Another strength is that by using the validated instrument NCSI we can compare our data with other studies that used this instrument.

Lower and higher [30] IFA cut-off values are internationally used for screening. Lacking an international standard we used the IFA value 1:64 that is commonly used in the Netherlands.

Another limitation of the study is that the fatigue status of participants before the outbreak is unknown, thus participants might already have been fatigued for other reasons before the outbreak took place. The use of a self-reporting questionnaire is also a limitation. Even though questionnaires were checked for missing information or errors by medical and paramedical staff, it was not possible to entirely prevent missing information. A not quantifiable recall bias is likely to have occurred for the following two reasons: perceived acute Q-fever episodes were reported with a time lag of four to seven years [31]. Furthermore, cross-sectional study designs with retrospective components have in general a higher risk of

recall bias [32]. An acute illness in the past could also have been erroneously reported by a participant as Q-fever regardless of the cause.

CONCLUSIONS

Seven years after the start of the Q-fever epidemic in the Netherlands, the prevalence of antibodies against *C. burnetii* among the adult population of an affected village was still 34%. A large proportion of the population reported an impaired health status with fatigue. However, there were no differences between those with and those without antibodies against *C. burnetii* for fatigue and other health status parameters.

Participants who had been notified for clinically apparent acute Q-fever, reported twice as much fatigue compared to those who had serological evidence of a past infection but who had previously not been notified because they did not fulfil the notification criteria or because they had experienced a mild or asymptomatic infection.

There are many reasons for fatigue and in some cases a Q-fever episode can be an attributing or causative factor. Even though some individuals developed fatigue after a *C. burnetii* infection the majority of individuals became fatigued due to other and often unknown reasons.

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APPENDIX SUPPLEMENTARY TABLES

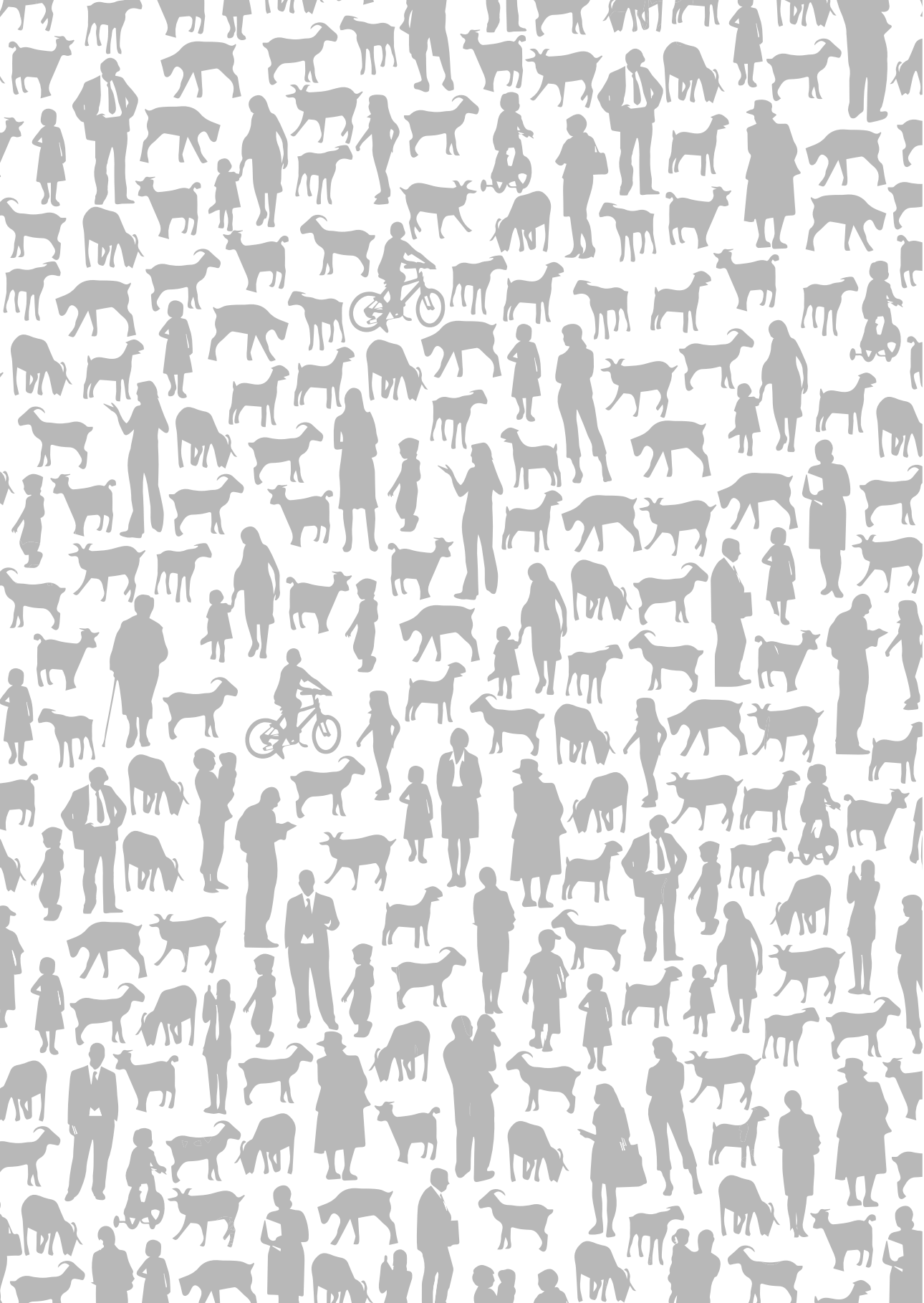
Supplementary Table S1. NCSI sub-domains divided in normal, mild and clinically relevant problems in relation to the IFA status[1].

Sub-domains	IFA positive		IFA negative		*p*-value
	n	*(%)*	n	*(%)*	
Subjective pulmonary symptoms	509		997		0.04
Normal	358	*(70.3)*	639	*(64.1)*	
Mild problem	104	*(20.4)*	232	*(23.3)*	
Clinically relevant problem	47	*(9.2)*	126	*(12.6)*	
Dyspnoea Emotions	507		994		0.05*
Normal	410	*(80.9)*	749	*(75.4)*	
Mild problem	52	*(10.3)*	134	*(13.5)*	
Clinically relevant problem	45	*(8.9)*	111	*(11.2)*	
Fatigue	482		942		0.45
Normal	311	*(64.5)*	576	*(61.1)*	
Mild problem	67	*(13.9)*	148	*(15.7)*	
Clinically relevant problem	104	*(21.6)*	218	*(23.1)*	
Behavioural Impairment	507		997		0.28
Normal	365	*(72.0)*	724	*(72.6)*	
Mild problem	113	*(22.3)*	198	*(19.9)*	
Clinically relevant problem	29	*(5.7)*	75	*(7.5)*	
Subjective Impairment	507		995		0.17
Normal	366	*(72.2)*	683	*(68.6)*	
Mild problem	113	*(22.3)*	233	*(23.4)*	
Clinically relevant problem	28	*(5.5)*	79	*(7.9)*	
GQOL	497		978		0.46
Normal	356	*(71.6)*	719	*(73.5)*	
Clinically relevant problems	141	*(28.4)*	259	*(26.5)*	
HRQOL	507		992		0.59
Normal	358	*(70.6)*	677	*(68.2)*	
Mild problem	90	*(17.8)*	184	*(18.5)*	
Clinically relevant problem	59	*(11.6)*	131	*(13.2)*	
Satisfaction relation	501		986		0.27
Normal	337	*(67.3)*	671	*(68.1)*	
Mild problem	107	*(21.4)*	182	*(18.5)*	
Clinically relevant problem	57	*(11.4)*	133	*(13.5)*	

[1]Analysed with the Pearson's chi-squared test. *The actual *p*-value is 0.054.

Supplementary Table S2.The IFA status and fatigue, stratified by perceived or known episode of acute Q-fever

		Total							
History acute Q-fever		**n=1413**	**Fatigue**	***(%)***	**No fatigue**	***(%)***	**OR**	**CI**	***p*-value**
Medically confirmed or perceived	**IFA positive**	137	67	*(48.9)*	70	*(51.1)*	0.60	(0.30-1.2)	0.17
	IFA negative	44	27	*(61.4)*	17	*(38.6)*			
	Total	181	94	*(51.9)*	87	*(48.1)*			
No or don't know	**IFA positive**	343	103	*(30.0)*	240	*(70.0)*	0.71	(0.54-0.93)	0.01
	IFA negative	889	335	*(37.7)*	554	*(62.3)*			
	Total	1,232	438	*(35.6)*	794	*(64.4)*			
Adjusted Mantel Haenzel Summary Chi Square test							0.69	(0.54-0.89)	0.67



Chapter 9

FATIGUE FOLLOWING ACUTE Q-FEVER: A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Background

Long-term fatigue with detrimental effects on daily functioning often occurs following acute Q-fever. Following the 2007-2010 Q-fever outbreak in the Netherlands with over 4000 notified cases, the emphasis on long-term consequences of Q-fever increased. The aim of this study was to provide an overview of all relevant available literature, and to identify knowledge gaps regarding the definition, diagnosis, background, description, aetiology, prevention, therapy, and prognosis, of fatigue following acute Q-fever.

Design

A systematic review was conducted through searching Pubmed, Embase, and PsycInfo for relevant literature up to 26th May 2015. References of included articles were hand searched for additional documents, and included articles were quality assessed.

Results

Fifty-seven articles were included and four documents classified as grey literature. The quality of most studies was low. The studies suggest that although most patients recover from fatigue within 6-12 months after acute Q-fever, approximately 20% remain chronically fatigued. Several names are used indicating fatigue following acute Q-fever, of which Q-fever fatigue syndrome (QFS) is most customary. Although QFS is described to occur frequently in many countries, a uniform definition is lacking. The studies report major health and work-related consequences, and is frequently accompanied by nonspecific complaints. There is no consensus with regard to aetiology, prevention, treatment, and prognosis.

Conclusions

Long-term fatigue following acute Q-fever, generally referred to as QFS, has major health-related consequences. However, information on aetiology, prevention, treatment, and prognosis of QFS is underrepresented in the international literature. In order to facilitate comparison of findings, and as platform for future studies, a uniform definition and diagnostic work-up and uniform measurement tools for QFS are proposed.

INTRODUCTION

Q-fever, caused by the Gram-negative intracellular coccobacillus *Coxiella burnetii,* is a zoonosis that occurs worldwide [1]. Between 2007 and 2010 the largest Q-fever outbreak ever described in the literature occurred in the Netherlands, resulting in 4107 notifications [2].

Fatigue following acute Q-fever, also referred to as Q-fever fatigue syndrome (QFS), has been described worldwide in up to 20%-30% of patients [3-8] and may last up to ten years or longer [7, 9]. Although some debated the term QFS [10], it has been frequently used throughout literature. QFS patients experience an impaired health status, pulmonary disorders, and impairment of general and social functioning [3, 7-9, 11, 12], and QFS accounted for major Q-fever-related economic cost during the Dutch outbreak [13]. Therefore, although not always recognised as a (diagnostic) problem, this sequel has major implications. The word "syndrome" refers to other frequently accompanying nonspecific symptoms [3, 8, 9, 14] resembling chronic fatigue syndrome (CFS) [15, 16]. However, in CFS the cause is usually unknown, while in QFS a *C. burnetii* infection can be identified as the trigger. Furthermore, QFS has a sudden onset of fatigue, while in CFS this is often not the case. Several queries regarding QFS without clear answers exist. A uniform international definition is not available, and tools to assess this syndrome and its consequences vary [5, 6, 17]. Hypotheses on aetiology appear contradictory [18], and vary from altered cytokine production [6, 19], development of symptoms determined by host and genetic factors [19-21], to the perpetuation of symptoms due to psychogenic factors and behaviour [8]. Furthermore, opinions on possible treatment of QFS differ [5, 6, 17], and questions exist regarding prevention and prognosis.

The aim of this first systematic review regarding fatigue after acute Q-fever in humans is to provide an overview of all relevant available literature, and to identify knowledge gaps regarding the definition, diagnosis, background, description, aetiology, prevention, therapy, and prognosis. This provides an evidence map both for physicians and patients.

METHOD

Search strategy and selection criteria

Relevant articles were identified through a systematic literature search in the scientific databases Medline, Embase and PsycInfo up to the 26th of May 2015 (*Table 1*). As Pubmed was used to search in Medline, only Pubmed is mentioned in this article. There were no restrictions on year of publication, language, and article or study type. Abstracts without full-text were excluded, as well as non-human studies. During the first selection step, potentially relevant references were selected based on screening of titles and or abstracts by two investigators independently (GM and SPK, both content area experts). Potentially relevant

articles were included for full-text assessment. Articles on fatigue following acute Q-fever that could provide information on the following domains: diagnosis (i.e. definition and/or diagnosis), background/descriptive (i.e. incidence, prevalence, the course of fatigue and the role of co-morbidity, and other complaints besides fatigue), aetiology (i.e. pathophysiology, predictors), prevention/therapy, and prognosis, were selected.

Table 1. Search strategy used in Pubmed, Embase, and PsycInfo

Pubmed	***Search terms†***	***Hits***
6-5-2014	("coxiella burnetii" OR "Q fever" OR "coxiella" OR "Q-fever" OR "rickettsia burnetii" OR "rickettsia burnetti" OR "rickettsiosis infection" OR "rickettsiosis rickettsia" OR "australian Q fever")	
	AND	
	("fatigue" OR "syndrome" OR "Q fever Fatigue Syndrome" OR "Q-fever Fatigue Syndrome" OR QFFS OR QFS OR persisten* OR progress* OR "long term" OR "long-term" OR consequence* OR "chronic fatigue" OR tired*)	**494**
26-5-2015		**537**
Embase	***Search terms†***	***Hits***
6-5-2014	(exp Q fever/ OR Q fever.tw. OR exp Coxiella/ OR coxiella.tw. OR rickettsia burnetii.tw. OR rickettsiosis.tw.)	
	AND	
	(exp fatigue/ OR exp Fatigue Impact Scale/ OR exp chronic fatigue syndrome/ OR exp Fatigue Severity Scale/) OR fatigue.tw. OR QFFS.tw. OR QFS.tw. OR exp persistent infection/ OR (persistence or persistent). tw. OR (progression or progressive or consequence or consequential). tw. OR exp chronic fatigue syndrome/ OR (tired or tired' or tiredeness or tireding or tiredness or tiredness).tw.	**440**
26-5-2015		**489**
PsycInfo	***Search terms***	***Hits***
6-5-2014	(Q fever OR coxiella OR rickettsia burnetii OR rickettsia burnetti OR rickettsiosis OR rickettsiosis rickettsia)	**15**
26-5-2015		**18**

Literature search performed on 6th May 2014, updated on 26th May 2015, using the same search terms as in the first search. † Excluded from the search: Mesh term for rickettsiosis, as this labels for several typhus infections with a total hits of 15600 records; and the word 'chronic', to avoid inclusion of chronic Q-fever articles

During the full-text assessment, articles without original or relevant data were excluded, upon an independent decision of each investigator, followed by consensus if needed. In case of any disagreement, the verdict of a third independent investigator was conclusive. If GM or SPK was a (co)author of a potentially relevant article, a third independent investigator

assessed and decided (both selection steps) on inclusion. GM and SPK translated non-English articles, if needed, native speakers where sought. If native speakers were unavailable, the corresponding author was contacted. If this yielded no response, the article was excluded.

Reference lists of included full-text articles were hand searched for additional relevant publications. If the title (or keyword in the title) suggested potential information on the topic, retrieval and full-text assessment followed. Finally, the World Health Organization, Centres for Disease Control and Prevention (CDC), Queensland Health, and gov.uk websites were searched for guidelines. Documents with relevant information that were identified during the search, but not classified as peer-reviewed articles, were included as grey literature.

Quality assessment

The methodological quality of case-control and cohort studies was assessed with the Newcastle-Ottawa Scale (NOS) [22], that evaluates selection (maximum of 4 stars), comparability (maximum of 2 stars), and outcome (maximum of 3 stars). For economic evaluations, the 'Evers checklist' was used [23]. Case-series were assessed with a quality appraisal tool with 18 criteria. A score of ≥14 criteria (≥70%) was considered acceptable [24]. No specific instruments exist to assess the quality of case-reports, which in general is considered to have a low level of evidence. Therefore, the quality was assessed with a method based on the Coordination of Cancer Clinical Practice Guidelines in Europe (CoCanCPG), addressing eight criteria: an appropriate and clearly focused question, representative population, description of the survey method or data collection, outcome measures defined and described, response rate reported, and results valid and applicable to the targeted patient group. Articles could score:-/-,-, +/-, +, or ++ on these items. Although personal opinions were included to obtain a complete overview of all literature, these were not quality assessed as in general the quality is considered low.

Data extraction and presentation

Study populations and definitions per included article were summarised in a separate table (*S1 Table*). Included articles were summarised in main domain tables: diagnosis, background/descriptive, aetiology, prevention/therapy, and prognosis (*S2-S5 Tables*). If articles contained additional information on other domains, this was noted in the main table. The following information was provided per article, if applicable: year of publication in chronological order starting with the oldest articles; first author; country; year of the study; study period and duration; study type; number of patients and controls; patient characteristics; co-morbidity; outcome measurement tools; intervention(s); outcome; conclusion(s)/recommendation(s); and the quality of the article. In case an article could not be assessed with any of the mentioned tools, this was stated in the table in column quality assessment (QA) as not applicable (NA). Grey literature was similarly ordered in a separate table (*S6 Table*).

RESULTS

Inclusion of articles

The search yielded 1044 references (*Fig 1*); Pubmed n=537, Embase n=489, PsycInfo n=18, of which 223 were duplicates. During the first selection phase, 680 references were excluded as not relevant, 141 identified as potentially relevant, and the full-text articles were searched. One full-text article (Spanish) could not be obtained from three different libraries and as the author could not be reached, the article was excluded. Three conference abstracts without full-text article were excluded. Of the remaining 137 full-text articles, 51 articles were deemed not relevant, 29 had no original data, and for three no translation was available (two Russian, one Japanese). The remaining 54 articles were included and hand searching their reference lists yielded 22 potentially relevant articles, of which three were included after full-text assessment. From the reference lists of included articles, we identified one guideline, one dissertation, two book chapters, and one economic report. After confirmation of relevance, these were included as grey literature except for one book chapter as retrieval was not possible. In total, we included 57 articles and four grey literature documents.

Classification in domains

The 57 included articles were classified into one of the main domains: diagnosis (n=4, *S2 Table*), background/descriptive (n=29, *S3 Table*), aetiology (n=18, *S4 Table*), and prevention/therapy (n=6, *S5 Table*). As none of the included articles described the course of fatigue in QFS, no articles were classified into the domain prognosis. Grey literature (n=4) is presented in *S6 Table*.

Quality of included literature

From the four articles in the table diagnosis, one article was assessed with the NOS and scored 4/9 possible stars [25]. The remaining items (five stars) could not be assessed, as these items were not applicable for this study. The other three articles were personal opinions [10, 26, 27].

The quality of 21/29 articles in the domain background/descriptive was assessed with the NOS. Most articles had a moderate quality; however, none scored on all specific applicable criteria, mostly because of inadequate controls in the design or analysis. For four articles, not all items could be assessed, as these were not applicable for these studies. The quality of three case-reports (n=1) was low [28-30]. The quality of one study regarding burden of disease was not assessed [31], as no standard quality assessment checklist was available for this study category. One economic evaluation scored well (16/19) [32]. Two articles were personal opinions [33, 34], and one was a personal observation [35].

The quality of 15/18 articles on aetiology was assessed with the NOS. Although none scored on all specific applicable criteria, the quality of the articles was considered moderate. Seven articles did not score on comparability although applicable, as they lacked a correction for other factors that might explain the outcome. For four articles, not all possible stars could be retrieved, as these items were not applicable for these studies. Two laboratory case studies were not quality assessed [36, 37], and one article was a personal opinion [38].

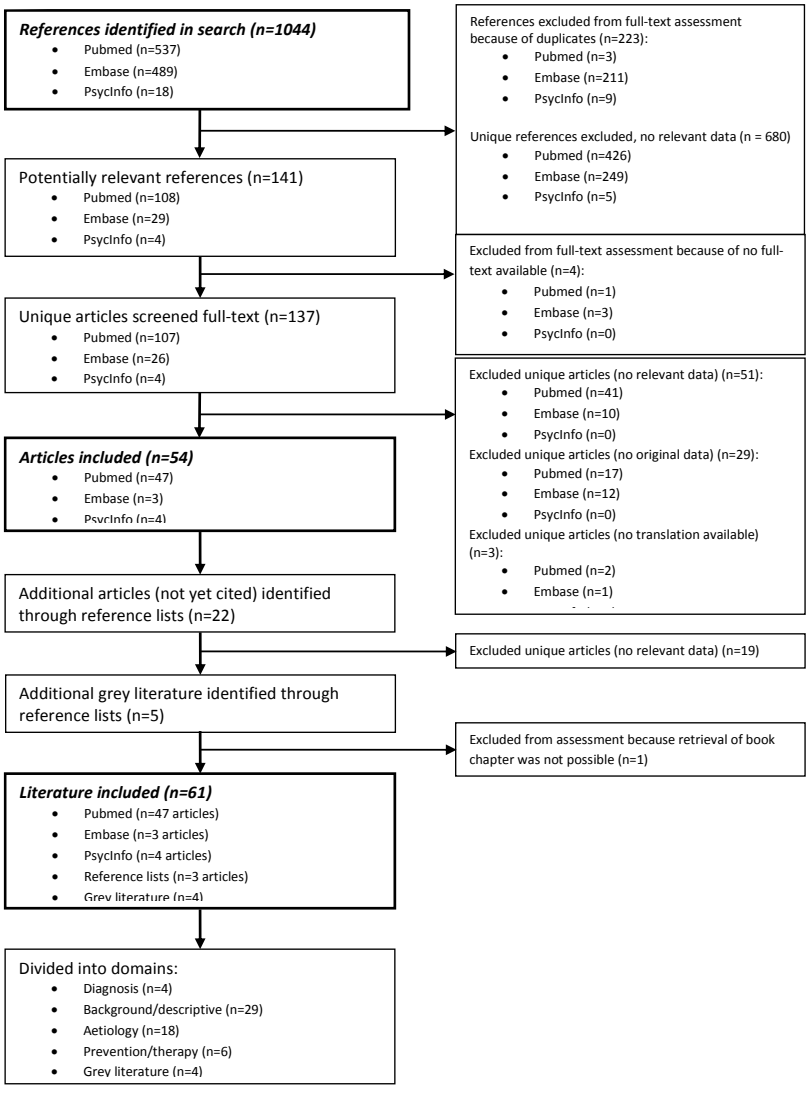

Fig 1. Flowdiagram of identified literature.

The quality of 2/6 prevention/therapy articles was assessed with the NOS. One study scored 4/9 stars, but none on comparability [39], while the other scored on 4/5 applicable items [6]. The quality of two case-reports (n=1) [40, 41] was below average, as was that of the case-series (n=3) [5], that scored on only 9/18 criteria. One article, a study protocol, was not quality assessed [42].

The Dutch QFS guideline was developed based on the AGREE criteria [43], and therefore considered to be of good quality [17]. The quality of the other grey literature was not assessed.

Definition and diagnosis

Nineteen articles contained information on diagnosis of which four were classified in the main table diagnosis (*S2 Table*) [10, 25-27].

Terminology. The name QFS was introduced in 1992 [44]. Ever since, it has been debated whether fatigue following acute Q-fever is a separate entity compared to other forms of post-infective fatigue or CFS [27]. Some argue that chronic fatigue is a non-specific subjective state or symptom after Q-fever rather than a diagnosis [27]. Other consider QFS as a description of CFS implicating a specific micro-organism, and that this terminology might result in increased health-care costs [10]. Others stated that due to convincing evidence of a causal factor, QFS is a causally-defined subset of CFS, and that this factor should take precedence in the diagnostic statement [26]. Names used to indicate fatigue following acute Q-fever, include: residual asthenia following Q fever [38], postinfective fatigue or postinfective fatigue syndrome [10, 12, 18, 31, 45-47], postinfectious chronic fatigue [11], post-Q-fever debility syndrome [35], post-Q-fever chronic fatigue syndrome [35], qCFS [36], Q fever induced chronic fatigue syndrome [48], post-Q-fever fatigue or post-Q-fever fatigue syndrome [36, 49], post-(acute) Q-fever (fatigue) syndrome [5, 14, 26, 28, 33, 50], and most frequently Q-fever fatigue syndrome (QFS or QFFS) [6, 8, 10, 19-21, 26, 30, 33, 36, 39, 42, 50-52].

In conclusion, the term QFS has been used for years and seems generally accepted.

Definition of QFS. An overview of the study populations and definitions used is provided for articles (*S1 Table*) and grey literature (*S6 Table*). Seven articles lacked a definition of the study population or of QFS [10, 26, 27, 33-35, 38]. In 32 articles the study population was defined but QFS was not [3, 7, 9, 11, 12, 14, 18, 25, 31, 32, 36, 37, 45-47, 49, 52-67]. In five articles individual patients were considered to have QFS, without providing a definition [5, 28-30, 40]. Six articles provided a definition of QFS [6, 8, 19, 39, 42, 48], which has been used in articles in subsequent years [20, 21, 50, 51]. A detailed description of QFS is published in a thesis [44], but is based on a retrospective comparative-cohort study and is not available online. In the Dutch QFS guideline [17], QFS is defined as: a severe fatigue causing significant disabilities in daily life present for at least 6 months, with a temporal relationship with acute

Q-fever, and not caused by co-morbidity. Fatigue should be absent before acute Q-fever or should have significantly increased since the infection.

In conclusion, there is no international uniform definition for QFS.

Diagnosis. No articles provided complete information on the diagnostic work-up. The Dutch guideline on QFS bases diagnosis on a combination of history, physical examination and laboratory examination excluding other causes of fatigue, and should at least include erythrocyte sedimentation rate, C-reactive protein (CRP), creatine kinase, thyroid stimulating hormone, leukocytes with differentiation, creatinine, alkaline phosphatase, alanin amino-transferase, calcium, glucose, ferritin, and a urinary sediment. Through the use of validated questionnaires fatigue severity should be objectified. Morbid obesity (BMI>40) and substance abuse should lead to refraining from diagnosing QFS. It is not possible to diagnose QFS in case of: depression (if this preceded current symptoms), schizophrenia, psychosis, dementia or eating disorders (unless already resolved for a minimum of 5 years) [17].

In conclusion, the Dutch guideline on QFS provides a clear diagnostic work-up.

Background/descriptive

Of the 40 articles containing background/descriptive information, 29 were classified in the main table background/descriptive (*S3 Table*) [3, 7-9, 11, 12, 14, 28-35, 52, 53, 56-59, 61, 62, 64-69].

Incidence and prevalence of fatigue following C. burnetii infection. Fatigue following acute Q-fever was first described in 1960 [68]. Without indicating a time-relation with acute Q-fever, it was noted in 1990 that 4% of acute Q-fever cases had prolonged fatigue [53]. In 1992, it was stated that approximately 23% of study subjects developed QFS within 12 months following acute Q-fever [44]. Ever since, several studies on fatigue following acute Q-fever reported different prevalences. It was stated that 5-10% of patients experience residual asthenia six months after acute Q-fever and only few after one year [38]. In a reaction, it was underlined that a substantial proportion of acute Q-fever patients have symptoms similar to QFS for 6-9 months after the acute infection and then recover, but 8-10% of patients exhibit symptoms for at least a year [33]. This is similar to other reports, showing persistent symptoms for longer than two years [3], up to six years after the infection with 66% of patients reporting fatigue [14]. In Australia, QFS is the most common sequel of acute Q-fever reported to affect 10-15% of patients [70]. Higher percentages were described, with up to 28% of patients meeting the Centres for Disease Control and Prevention criteria for CFS 5 to 14 years after acute Q-fever, compared to none in the control group [8, 15]. The highest percentage of reported fatigue was 69% five years after acute Q-fever [9]. CFS criteria were met by 42% of *C. burnetii*-infected patients and 26% of controls [9, 15]. Ten years after acute Q-fever, 68% of patients reported fatigue of any duration [54], of whom 20% met the CFS criteria [15]. Excluding co-morbidity, 8% of patients met the CFS criteria compared to none of

the controls [54]. *C. burnetii*-exposed compared to non-exposed subjects reported ten years later a fatigue prevalence of 65% vs. 35%, respectively, and 19% vs. 4% met the CFS criteria [7, 15]. In accordance, later results demonstrated fatigue to be more common after Q-fever compared to controls [58], up to two [61] and six years later [49, 69].

Post-infective fatigue following *Epstein-Barr virus*, *Ross River virus* or *C. burnetii* infection, was reported in 35% of cases after six weeks, 27% after three months, 12% after six months, and 9% after 12 months, regardless of the infective agent [12]. And, although not significantly different, 12 months after acute Q-fever, patients were more fatigued than after Legionnaires' disease, while being younger and having less pre-existing health problems [11]. In patients with a lower respiratory tract infection who were *C. burnetii* seropositive 10-19 months after the acute illness, 40% reported clinically relevant fatigue, compared to 64% of seronegatives, concluding that patients have long-term health problems after a lower respiratory tract infection in general [64].

In conclusion, fatigue following acute Q-fever might not be specific but occurs frequently and may persist for years. A large variance in prevalence of fatigue after Q-fever is reported between countries, due to differences in definitions, study designs and populations, and measurement tools, which impairs direct comparisons.

Health status, burden of disease and economic impact. A sustained decrease in health status or health-related quality of life was reported [3, 58, 61]. Twelve months after acute Q-fever, 50% of patients had a reduced general quality of life [11]. Other studies show a significant linear improvement in health status after acute Q-fever, but it was still reduced after 24 months in more than one third of all patients [67]. Twenty-seven months after acute Q-fever, 52% of patients reported persistent symptoms and lower scores on 5/8 Short Form 36 (SF-36) scales [71] compared to uninfected controls [3]. Four years after acute Q-fever, patients also had a significantly reduced health status compared to healthy controls [65]. To obtain a detailed overview of the patients' health, a combination of the complete Nijmegen Clinical Screening Instrument (NCSI) [72] with subdomains (Role Physical, Bodily Pain, Social Functioning, and Role Emotional) of the SF-36 was advised [25]. Two studies focus on the burden of disease of fatigue following acute Q-fever [31, 32], one also assessed the economic impact of the outbreak in the Netherlands [13]. In 1992, for Australian *C. burnetii*-infected abattoir workers the costs per year for medical care and loss of wages for endocarditis and for QFS were calculated [44]. QFS represented the largest burden of disease [32, 44]. Furthermore, others found that, although the number of disability adjusted life years was higher for influenza, on a per case basis, Q-fever was more severe, and overall the burden of disease was more than eight times higher than for influenza, due to long-term sequelae [31]. The estimated income loss was largest due to the accumulation over time as a consequence of the projected duration of sick leave, and QFS was estimated to be one of the major Q-fever-related economic cost during the Dutch outbreak [13].

In conclusion, there are clear indications that fatigue following acute Q-fever results in a high burden of disease, a major negative impact on the health status of patients, and has significant economic implications.

Work-related consequences. In 1960, it was noticed that the majority of acute Q-fever patients recovered within weeks and returned to work [68]. However, this convalescence period was prolonged in 25% of cases who were absent from work for more than 6 weeks, 20% longer than 8 weeks, up to 23 weeks [68]. The mean period of sick-leave increased with age [68]. Later studies revealed that following acute Q-fever, 40% of patients were absent from work for more than one month [62]. After 12-26 months 9% was unable to function at premorbid levels due to fatigue and diminished concentration while more than 30% had not fully resumed daily activities, in 81% due to fatigue [62]. Besides work-related consequences, patients were more likely to report functional impairment in performing daily activities than healthy controls [46]. Q-fever patients showed a reduced work participation, from 45% after three months to 19% after 12 months, versus 15% of patients with Legionnaires' disease after 12 months [66]. Factors associated with reduced work participation were: having symptoms; a higher level of sorrow; being a former smoker (compared to never smoking); not consuming alcohol; and receiving treatment for health-related effects of Q-fever [66].

In conclusion, the majority of patients return to work within the first 12 months after acute Q-fever, although up to 20% reported reduced work participation.

Course of fatigue following acute Q-fever and the role of co-morbidity. Following acute Q-fever, 69% of patients self-reported fatigue, which dropped to 52% at six months to 26% at 12 months [57]. Studies using the NCSI found that severe fatigue following acute Q-fever improved from 73% at three months, to 60% at 12 months [11, 67]. Twelve to 26 months after acute Q-fever up to 59% of patients reported fatigue of which 44% had severe fatigue [59], whilst after 24 months 37% of patients compared to 3% of healthy controls, reported severe fatigue [67]. Higher rates of 51% were described four years after infection [65]. Most articles describe a continuous fatigue syndrome, up to 74 months after the initial infection [19], while relapsing or remittent fatigue patterns also seemed to occur [3], up to 57 months [19] after acute Q-fever. One article reported a fatigue free period of 2-4 months after acute Q-fever, eventually followed by QFS [5]. A disease period up to 20 years has also been reported [44]. Pre-existing health problems were associated with a long-term reduced health status including fatigue [59, 62, 67].

In conclusion, the percentage of patients who experience severe fatigue following acute Q-fever slowly decreases over time, mainly in the first 6-12 months. Fatigue remains a persistent complaint in approximately 20% of patients, with varying percentages and variability in the reported course of fatigue following acute Q-fever, and may persist for up to 20 years.

Complaints besides fatigue. QFS is frequently compared to CFS, and patients who fulfil the international CFS criteria by definition have multiple symptoms [15, 16]. The mean num-

ber of symptoms was higher in Q-fever exposed subjects 10 years after exposure compared to controls [7]. Patients with post-infective fatigue, including Q-fever-related post-infective fatigue, reported more symptoms in general and fatigue-related symptoms in particular [46]. Twelve to 26 months after acute Q-fever 40% of patients reported additional complaints [62]. An overview of frequently reported complaints besides fatigue after acute Q-fever is given below.

Musculoskeletal complaints. Myalgia and arthralgia were frequent complaints of patients considered to have QFS [5, 6, 17, 28, 39, 40, 44, 70]. Musculoskeletal pain accompanied fatigue 12 months after several infections [12], and was associated with a higher age [18]. Myalgia was significantly more often present 5-14 years after acute Q-fever compared to controls [8]. Twelve to 26 months after acute Q-fever, 4% of patients reported myalgia [62]. Myalgia was a major complaint in 23% of working patients 12 months after acute Q-fever [66]. Arthralgia was reported by 69% of patients up to six years after acute Q-fever [14], and was more severe compared to controls [9]. Both myalgia and arthralgia were also described in up to 70% of patients after a laboratory documented *C. burnetii* infection [52]. Compared to controls, presumed QFS patients had a higher pain score [48].

Neurocognitive problems. Although some authors found no association between *C. burnetii* seropositivity and concentration difficulties [56], neurocognitive difficulties were described in patients with post-infective fatigue, including QFS patients, 12 months after primary infection [12]. In addition, older subjects reported more neurocognitive symptoms [18]. Twelve to 26 months after acute Q-fever, 4% of patients had difficulties concentrating [62]. Concentration and memory problems were also shown to be a major complaint in 24% of working Q-fever patients 12 months after the infection [66]. Although no difference was found in the frequency of memory problems between cases and controls, the severity was significantly higher after Q-fever [9]. A lack of concentration and short memory impairment within a year following acute Q-fever was also reported [17, 44], while another study found decreased concentration and mental acuity that could last up to 5-10 years [70].

Sleeping problems. Six years after acute Q-fever, 65% of patients reported a disturbed sleep pattern, which was significantly more frequent than in controls [14]. This was also reported by others [17, 29, 44, 70], including unrefreshing sleep [5].

Headache. Headache was frequently reported [5, 6, 17, 28, 30, 39, 52, 68, 70]. Twelve months after acute Q-fever, 24% of working patients reported frequent headaches [66]. Another study reported headache in 47% of patients six years after acute Q-fever [14]. Although the frequency of headache was similar to controls, the same authors found that the severity of headache was more profound in those after Q-fever [9].

Blurred vision. Blurred vision six years after acute Q-fever was similar to controls [14], but was more prevalent and more severe five years after acute Q-fever compared to controls in

another study (34% vs. 18%) [9]. Blurred vision was also reported by others [17, 44]. Visual complaints were noted by 2% of patients 12 to 26 months after acute Q-fever [62].

Increased (night) sweating. Night sweats starting 6-12 months after acute Q-fever were described [70]. Twelve to 26 months after acute Q-fever, 3% of patients reported night sweats [62]. In comparison to controls, night sweats were more common after acute Q-fever [17, 44, 70]. Most QFS patients had this symptom for 5-10 years [70], up to 14 years [8, 28]. A combination of night sweating and increased sweating was also reported [30]. Increased sweating occurred with 53% more frequent after acute Q-fever compared to controls [14]. Others reported 53% of cases with increased sweating [5, 9]. Some authors considered abnormal sweating at least ten times a year as major QFS symptom [44].

Respiratory tract problems. Following acute Q-fever, 9% of patients complained of persistent chest symptoms [53]. Others reported that 47% of presumed QFS patients complained of cough and a sore throat with a mean symptom duration of four years [52]. Others reported these complaints also [17, 28-30, 39]. Five years after acute Q-fever, 51% of cases complained of breathlessness on exertion [9], compared to 32% of controls. Six years after acute Q-fever, 59% of patients complained of cough, 49% of breathlessness, and 51% of chest pain, all significantly more frequently than controls [14]. Furthermore, an association between QFS and bronchial asthma has been suggested [30].

Mood disorders. Patients with fatigue after acute Q-fever have been reported to experience increased irritability [14], mood disturbances [12, 17], and anger [70]. Mental problems, e.g. depression and unstable moods, can occur within a year following acute Q-fever [44], whereas, with regard to depression, most subjects were healthy before the infection [44]. Two years after acute Q-fever more psychosocial complaints were observed compared to controls [61]. Common symptoms of psychological distress were reported significantly more in patients with post-infective fatigue, including QFS patients, compared to healthy controls [46]. Others hypothesise that Q-fever-related fatigue might be explained by psychological distress, caused by uncertainty about their illness and repeated medical contacts that reinforce perceptions of ill health [7]. Some contradict this hypothesis [67]. Infection with *C. burnetii* was followed by depression in 10% of cases [53]. Three case-reports (all n=1) [28-30] reported a *C. burnetii*-triggered depression, leading to thoughts of death [28], a near suicide attempt [30], and suicide [29]. The suggestion was that cytokine network abnormalities after a *C. burnetii* infection might underlie the onset of depression [28, 29, 73]. Although a possible relationship between high IgG phase II *C. burnetii*-antibodies and depression was suggested [69], others found no association between seropositivity, and depression, depressive ideas or overall psychiatric morbidity [56].

Other complaints. Other reported symptoms accompanying prolonged fatigue after Q-fever are severe malaise [40, 41], setback upon exertion and the need for prolonged rest after simple tasks [5, 8, 68], poor appetite [30, 68], gastrointestinal symptoms [6, 17, 29,

30, 44, 70], muscle fasciculation or spasms [8, 17, 41, 44, 70], dizziness [14, 17, 30], light intolerance [8, 19], tinnitus [28], taste disturbance [28, 29], loss of libido [17, 19], nasal and bronchial congestion [8, 17], and enlarged or painful lymph nodes [17, 70]. Bradycardia was postulated as a sign of QFS [35], and palpitations were described [30]. Even though reported in several studies [8, 17, 19, 44], alcohol intolerance was not statistically more frequent in the Q-fever group six years after acute Q-fever when compared to controls [14]. A slightly elevated body temperature (below 38 degrees Celsius) was described in QFS patients [5, 6, 28, 30, 39-41, 44, 70]. Up to 53% of assumed QFS patients felt feverish for four years [52].

In conclusion, besides fatigue as the main complaint, several nonspecific symptoms accompanying fatigue following *C. burnetii* infection were described. Commonly reported symptoms include musculoskeletal complaints, neurocognitive symptoms, sleeping problems, headaches, blurred vision, increased (night) sweating, respiratory complaints, and mood disorders.

Aetiology

Of the 28 articles that contained information on aetiology, 18 were classified in the main table aetiology (*S4 Table*) [18-21, 36-38, 45-51, 54, 55, 60, 63].

Pathophysiology. Genetic variance and relationship with fatigue**.** No relation [3] or correlation [47] between genetic factors and QFS was found. A lack of a coherent set of gene expression correlating across cohorts argued against the genetic signature for post-infective fatigue or CFS [47]. In contrast, another study found similar gene expression patterns for QFS and CFS patients [48]. The frequency of human leukocyte antigen – group DR (HLA-DR)-11 was significantly increased in QFS patients compared to controls. Also, more polymorphic variants within the NRAMP1 gene differing from the wild type were found, as well as significant differences in allelic variant frequencies within interferon-γ (IFNγ) genes, but effects were thought to be multigenic and cumulative. It was hypothesised that QFS might result from individual variations in immune response to *C. burnetii* [50]. QFS patients differed in the frequency of HLA-DRB1*11 carriage and the 2/2 genotype of the IFNγ intron 1 microsatellite compared to control groups [51]. Carriage was associated with reduced IFNγ and interleukin(IL)-2 responses from stimulated peripheral blood mononuclear cells (PBMC) [51].

In conclusion, results regarding genetic variations in host immune responses in QFS were contradictory.

Immunological aspects. An immunological basis for QFS or other post-infective fatigue syndromes was debated in several articles. A reduction in reported fatigue correlated with improvement in the delayed-type hypersensitivity skin response and general health scores [45]. Resolving fatigue after acute infection seemed associated with improved cell-mediated immunity, supporting an immunological basis for post-infective fatigue [45]. Upregulation of 2',5'-oligoadenylate synthetase (2-5AS) activity in PBMC of CFS patients was present, but a

relation between *C. burnetii* antibody titres and 2-5AS activities lacked [55]. It was however suggested that *C. burnetii* infection is associated with 2-5AS activities in some CFS patients, as 2-5AS activities changed from positive to negative in one CFS patient when *C. burnetii* antibodies disappeared [55]. In acute Q-fever IL-6 and CRP seemed predictive of more severe disease, but no support was found that these were associated with prolonged fatigue [63]. Markers of inflammation and pro-inflammatory cytokine concentrations did not remain altered in patients with post-infective fatigue [12, 18].

In conclusion, no clear evidence exists with regard to an immunological basis involving 2-5AS, IL-6, and CRP for the development of QFS.

Immunomodulatory complex and cell-mediated immunity. Persistence of *C. burnetii* or its antigens resulting in chronic immune stimulation with subsequent fatigue [8, 19-21, 36, 37, 49], or causing dysregulation of the macrophage/T-lymphocyte axis with subsequently aberrant monokine and lymphokine production mediating symptoms [8], was hypothesised. Cytokine release patterns of PBMC of QFS patients were aberrant with an accentuated IL-6 release, a decreased number of IL-2 responders, and an increased number of IFNy responders [19]. *In vitro*, using human samples, an increased cellular immune response and cytokine dysregulation was found with increased levels of IL-6 and IL-10, and decreased level of IL-2 [70]. A significant correlation between IL-6 and scores for key and total symptoms was found [19]. The detection of low levels of *C. burnetii* DNA in bone marrow aspirates, thin needle liver biopsies, and blood mononuclear cells, supports cytokine dysregulation and immunomodulation caused by *C. burnetii* persistence [20]. Others showed a more complex interaction between host-regulated disease and persistent *C. burnetii* DNA carriage- either live, dormant, or dead but with undegraded DNA - in bone marrow, irrespective of clinical state [21]. An additional but variable factor of host regulation of cell-mediated immunity was postulated, determining the level of persistence and symptomatic outcomes. It was hypothesised that in Q-fever without sequelae, the process of multiplication of live *Coxiella* was largely confined to bone marrow, in contrast to QFS, in which a modulated immune response caused increased levels of *C. burnetii* genome in bone marrow with increased shedding into peripheral blood [21]. Subsequently, one of the core hypotheses postulated included the presence of an immunomodulatory complex, consisting of non-viable undegraded *C. burnetii* DNA or its antigens, causing an abnormal cell-mediated immune response via damaged macrophages [37]. This stops the patient from clearing the microbe completely, leading to ongoing production of pro-inflammatory cytokines and subsequently fatigue. In contrast to QFS patients, those who fully recovered from acute Q-fever had no immunomodulatory complex [37]. The bacteraemia is restricted by humoral and cell-mediated immunity, by clearing of *C. burnetii* DNA containing components with an immunomodulatory effect of cell-mediated immunity and dendritic cells causing dysregulation, cytokines and other immune mediators, giving rise to symptoms [70]. The complexes appeared more likely to be a residue of the original heavy

seeding during the bacteraemia of the acute infection, rather than the product of an ongoing multiplication, destruction and renewal of infection [21]. QFS follows clinical overt infection, rarely subclinical infection, and the systemic symptoms of QFS may reflect a wide distribution of parasitized mononuclear phagocytes [36, 37]. In other patient cohorts, neither viable *C. burnetii* nor DNA in PBMC was detected [49].

In conclusion, several studies point towards cytokine dysregulation mediating symptoms in QFS. This may originate from an immunomodulatory complex consisting of non-viable undegraded *C. burnetii* DNA or its antigens. However, results regarding remnant *C. burnetii* DNA were contradictory.

Cardiac involvement in QFS. No ECG abnormalities excess in the *Coxiella*-exposed cohort with fatigue was found in comparison to controls [54]. Post-infective fatigue was associated with higher heartbeat discrimination accuracy, increased resting heart rate with decreased heart rate variability, and a lower pressure pain threshold [46]. The altered cardiac response was believed to be a stress response portraying an over-responsive system lacking dynamic flexibility [46]. Heightened interoceptive sensitivity with strong symptom correlation was also found. This suggests physiological hyper-vigilance and response inflexibility in post-infective fatigue [46].

In conclusion, there is no evidence for direct cardiac involvements in QFS, but there is some evidence for physiological hyper-vigilance and response inflexibility in patients with post-infective fatigue.

(Bio)psychological origin of QFS. It is unknown whether chronic fatigue following Q-fever is directly caused by the bacterium or if it is (bio)psychological in origin [38]. As subjective symptoms are difficult to quantify, it was stated that they might reflect an observational bias, *C. burnetii* strain or cultural differences, or genetic susceptibility [38]. In addition to the immune stimulation hypothesis, interpretations range from compensation-driven through psychogenic perpetuation of original symptoms or depression [8]. Q-fever patients with fatigue symptoms had higher somatisation scores, a higher tendency for hypochondriac worries and beliefs, a higher level of psychosocial complaints, and reduced quality of life [61]. The non-proven presumption was that Q-fever triggered fatigue development and that the risk of developing symptoms might be increased by hypochondriac features and a tendency to somatisation, supporting a biopsychological aetiology [61].

In conclusion, some studies supported the view of a biopsychological aetiology of QFS.

Predictors of post-infective fatigue syndrome, including QFS. Psychological factors and demographics. Post-infective fatigue appeared to be stereotyped across different infective triggers, and it was suggested that the host response rather than psychological or microbial factors determined ongoing symptoms [18]. No source of exposure was associated with developing persistent symptoms [3]. Premorbid and intercurrent psychiatric disorders were not predictive for post-infective fatigue [12]. In contrast to the biopsychological aetiology [61], it

was recently suggested that psychological distress was not an important factor in explaining increased fatigue levels after acute Q-fever [67]. Although some found that gender was not a predictor [12], others found an overrepresentation of women in high severity groups for fatigue, mood disturbance and neurocognitive difficulties [60]. Being female or a young adult, and smoking were characteristics significantly associated with long-term reduced health status including fatigue [62, 67]. In contrast, another study found no association between fatigue and age [59].

In conclusion, neither psychological nor microbial factors seem to predict post-infective fatigue, including QFS.

Severity of the acute illness. It was stated that one of the key risk factors for the development of post-infective fatigue, including QFS patients, is the severity of the acute illness [12]. Patients with post-infective fatigue had a longer mean duration of the acute illness, and more days in bed and days out of role during the acute phase compared to controls [18].The clinical expression of acute Q-fever seemed an essential factor in the subsequent sustained decrease in health status [58], which is supported by the finding that QFS usually follows acute Q-fever and rarely if ever asymptomatic infection [70]. Pre-existing health problems [62, 67], and hospitalisation, as an indicator of the severity of the initial infection, were also fatigue predictors [59, 62]. No symptoms during the acute Q-fever infection were predictors for persisting symptoms [3], nor did these determine the long-term health status [65]. Neither IL-6 and CRP levels nor antibiotic treatment during the acute infection were predictors for the development of prolonged fatigue [3, 63]. No relationship was found between fatigue and antibody titres six years after the Q-fever infection [49].

In conclusion, the severity of the acute Q-fever infection seems a key factor for worse long-term health status, including fatigue and QFS.

Genetic factors in predicting fatigue. A single nucleotide polymorphism (SNP) of the T allele IFNy+874T/A appeared to be the best predictor of increased fatigue after the acute phase of several infections, including *C. burnetii* [60]. While the C allele of IL-10-592C/A SNP exerted a protective effect on neurocognitive difficulties, the A allele IL-10-592 SNP and G allele IL-6-174G/C SNP were associated with increased mood disturbance [60].

In conclusion, as evidence is scarce, more research is needed regarding genetic factors predicting fatigue in QFS.

Prevention/therapy

Eleven articles contained information on prevention/therapy of which six are classified in the main table prevention/therapy (*S5 Table*) [5, 6, 39-42].

Prevention. No articles on the prevention of QFS were found. The Dutch guideline on QFS proposes to advice patients within the first six months after acute Q-fever or after established QFS to: i) stay mentally and physically as active as possible, adjust pace if necessary;

ii) alternate activities, also within activities; iii) keep fulfilling the role in daily life; iv) maintain a regular sleep-wake pattern; v) avoid focusing on fatigue; and vi) focus on feasible activities and appreciate accomplishments [17]. It is also proposed to explain that most patients recover within the first 6-12 months following acute Q-fever.

Antibiotic treatment. Four articles reported on the effect of long-term antibiotic treatment in assumed QFS patients [5, 6, 39, 40]. No randomised controlled trial (RCT) was found. Treatment with either 3 months of minocycline 200mg/day (n=18), levofloxacine 200mg/day (n=1), or erythromycin 400mg/day (n=1), improved performance status and reduced fatigue [6], concluding that minocycline was useful in treating QFS [6]. In a pilot-study, treatment with three months of minocycline 100mg/day (n=29), doxycycline 100mg/day (n=26), or levofloxacin 200mg/day (n=3), showed improvement in performance status, headache, and mean weekly temperature [39]. A case-series (n=3) [5] and case-report (n=1) [40] showed inconsistent results of treatment with long-term antibiotics. According to others, the positive effect of antibiotic treatment for QFS is not confirmed nor advised [17]. The efficacy of long-term antibiotic treatment is now tested in a RCT but results are not yet available [42].

In conclusion, available data on long-term antibiotic treatment for QFS are scarce and inconsistent.

Cognitive behavioural therapy (CBT) and graded exercise therapy (GET). CBT proved effective in reducing symptoms and improving functioning in CFS patients [74, 75], and in chronic fatigue in chronic illnesses [76-78]. It was suggested as treatment option for QFS patients who experience psychological distress [61]. Based on CFS literature and similarities between CFS and QFS, CBT is advised in the Dutch QFS guideline, although suspected not to be beneficial for all patients [17]. The effectiveness of CBT treatment for QFS is currently under investigation [42]. Also GET is recommended for QFS patients, as proven effective in reducing fatigue in CFS [17].

In conclusion, although evidence is lacking, CBT and GET might be effective in reducing fatigue in QFS patients.

Treatment of QFS-related symptoms. Three articles (all n=1) reported treatment of QFS-related symptoms [28-30]. The authors concluded that education and counselling about QFS and QFS-related symptoms should be provided to QFS patients [28]. Attention to the patient's mental state is necessary in order to recognise accompanying symptoms, e.g. depressive thoughts, that should be treated [30], and involving a psychiatrist early ought to be considered [29]. This has been recognised before, where tricyclic antidepressants were beneficial treatment of mental problems after acute Q-fever [44].

In conclusion, education and counselling of patients about QFS and QFS-related symptoms seems important, as well as considering a patient's mental state.

Alternative treatment. Alternative therapies for QFS patients were described (both n=1), including Kampo formula Tsumura Hochu-ekki-To granules, which appeared not to be effec-

tive [40], and Kampo formula Shakuyaku-Kanzo-To granules, which resulted in alleviation of stiffness in hand and arm [41].

At present, evidence for the use of alternative treatment lacks.

DISCUSSION

This first systematic review on fatigue following acute Q-fever, includes 57 articles and four grey documents up to the 26th of May 2015. The main limitation is the lack of a uniform definition of fatigue after Q-fever and the absence of a standardized diagnostic tool. In addition, the terminology both for fatigue and *C. burnetii*-related fatigue differed between publications and in time. Consequently, comparison of outcomes is difficult or impossible. Although not all articles could be quality assessed, these were nevertheless included as their information was considered valuable.

An international uniform definition of QFS, discriminating fatigue caused by *C. burnetii* from other post-infective fatigue syndromes and CFS is unavailable [19, 26, 36]. As the Dutch QFS guideline provides the most detailed description of QFS [17], we propose to use its definition and diagnostic work-up internationally. An international uniform definition provides the opportunity to achieve uniformity in diagnosis, treatment, and comparison of research results. It also provides recognition for physicians and acknowledgement for patients, reducing fear concerning uncertainty about their disease, providing an opportunity to continue their path to recovery [79, 80].

Whether fatigue following acute Q-fever is a separate entity compared to other forms of post-infective fatigue is debatable [10, 12, 18, 27, 44, 47, 81], but should not hamper the use of the term QFS.

Although differences in incidence and prevalence were reported, approximately 20% of patients remain chronically fatigued following an acute Q-fever infection. These differences can be explained by lack of recognition, uniform definition and diagnostic work-up, follow-up, and assessment tools. Using similar validated screening instruments is essential to compare studies [34]. Therefore, we advocate using validated screening instruments for measuring fatigue severity and disabilities, preferably with international available instruments [82], such as the Checklist Individual Strength or Chalder Fatigue Scale for fatigue [83, 84], and the NCSI, SF-36, or Sickness Impact Profile for disabilities [71, 72, 85]. This also helps to map the impact of QFS. The cut-off period of 6 months to diagnose QFS has been proposed as most patients recover spontaneously within this period, which corresponds with the internationally accepted definition for CFS [15, 16]. In QFS, fatigue frequently lasts beyond a year and mostly more than 5 to 10 years [8, 14]. Many nonspecific symptoms described accompanying fatigue in QFS were not systematically monitored as prospective data were unavailable. Most

studies did not report the time-relation between these symptoms, fatigue, and the Q-fever infection, nor the frequency of occurrence. Therefore, it was not possible to list all symptoms possibly related to fatigue following *C. burnetii* infection nor provide a temporal or causal relationship. However, guidelines with regard to the examination of chronic fatigue should be followed to rule out other diseases which can cause chronic fatigue.

Several hypotheses regarding the underlying pathophysiological mechanism of QFS were proposed, but no conclusive answers have been identified yet. Research on the relationship between genetic factors and QFS is contradictory and scarce. Several studies point towards cytokine dysregulation mediating symptoms in QFS, including an immunomodulatory complex consisting of non-viable undegraded *C. burnetii* DNA and or its antigens. However, these results need further confirmation, as most studies regarding this topic have been done by the same study group and contradictory results exist with regard to the presence of *C. burnetii* DNA in QFS. Several queries exist regarding predictors of QFS. Neither psychological nor microbiological factors seemed to predict post-infective fatigue. Only the severity of the acute Q-fever infection appears a predictor of long-term reduced health status.

No uniformity exists regarding optimal treatment for QFS. Results from RCTs using long-term antibiotics are not available, and the available studies all suffer from several important limitations, such as the lack of a clear QFS description, the inclusion of patients with a symptom duration of 1-4 months, and the inclusion of patients with positive *C. burnetii* PCR at baseline, possibly indicating chronic Q-fever, and can therefore not be generalized. As the evidence of beneficial antibiotic treatment in QFS patients lacks, it should not be prescribed for QFS patients. The recommended treatment after diagnosis of QFS in the Dutch QFS guideline is based on CFS literature, and consists of CBT and, if available GET. The effectiveness of these treatments in QFS has not been proven yet. A randomised placebo-controlled trial in order to evaluate the efficacy of both long-term doxycycline and CBT in QFS patients is currently performed [42]. Treatment should at least focus on the provision of medical care, physical rehabilitation and additional psychological support [81]. Furthermore, physicians should be aware of accompanying complaints, especially depressive thoughts, which require treatment at an early stage [29]. Alternative treatments were only effective in one case-report and are therefore not recommended. Finally, the prognosis of QFS patients is unclear regardless if treated or not.

In conclusion, the occurrence and long-term persistence of fatigue following acute Q-fever, generally referred to as QFS, has major health-related consequences. Information on aetiology, prevention, treatment, and prognosis of QFS is underrepresented in the international literature. In order to facilitate comparison of findings, and as a platform for future preferably prospective studies, we propose a uniform definition of QFS and the use of uniform measurement tools. In addition, in order to facilitate comparison of long-term sequelae following several infectious agents, and as a platform for further preferably prospective studies, an in-

ternational collaboration and a research agenda are desirable with regard to micro-organisms known for causing post-infective fatigue, in which *C. burnetii* should undoubtedly be included.

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SUPPLEMENTARY FIGURES AND TABLES

S1 Figure

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	172
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	172
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	173
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	173
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	173-4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	174-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	173-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	173-4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	173-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	173-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	173-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	173-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	173-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	173-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	176-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary tables
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	176-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	176-89
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	176-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	189-90
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	189-90
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	189-90
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	See financial disclosure section of the online submission system

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

S1 Table. Overview of study populations and used definitions

Included articles	Study populations and used definitions
1960, O. Powell [68]	1-2 yrs post AQF (AQF confirmed by demonstration CFT to *C.b.* with either a rise from zero to ≥1:32, or a titre in a single specimen of ≥1:256 in patients admitted to hospital or suspected of infection late in the illness) from Princess Alexandra Hospital, Brisbane. No definition for QFS or fatigue
1990, S. Reilly [53]	All AQF cases diagnosed and monitored by the Public Health Laboratory in Plymouth between 1972 and 1988 out of FUO, respiratory infections, CNE, and hepatitis cases. Clinical and serological status assessed in 1989. AQF: ≥fourfold rise in phase II titre, or by a stable phase II titre ≥80 if there was strong clinical evidence of AQF. Past infection: evidence of past exposure to *C.b.* by single or sustained phase II titres ≥10 to ≤40, with QF not being considered to be causally related to the presenting complaint. No definition for fatigue
1995, P. Harvey-Sutton [35]	No study population or QFS definition
1996, B. Marmion [8]	5-14 yrs post laboratory-proven AQF (AQF defined as a CFT titre of ≥1:256 or a 4-fold rise in phase II antibodies), QFS defined as: 1) incapacitating fatigue requiring prolonged rest after simple tasks; 2) nausea, persistent headache; 3) feeling feverish with profuse, odoriferous sweats at night, usually afebrile; 4) myalgia in any muscle group; 5) intermittent fasciculation of muscle fibres and muscle tenderness on palpation; 6) arthralgia without swelling, in any joint including costochondrals; 7) ethanol intolerance compared with capacity before AQF; and 8) interrupted sleep patterns, excessive and unreasonable irritability, unreliable short-term memory, and poor concentration. Less frequent complaints: bloating, irritable bowel syndrome, nasal and bronchial congestion, blurred vision, bright light intolerance, and enlargement and pain in lymph nodes. Definition CFS: according to the 1994 international CFS criteria [15]
1996, J. Ayres [14]	6 yrs post AQF [86, 87] (AQF defined as a CFT titre of ≥1:256 or a 4-fold rise in phase II antibodies), no QFS definition, but rather description of complaints being significantly more prevalent in past QF cases i.c.w. controls: joint pains, sleep disturbance, cough, sweating, irritability, chest pain, breathlessness, and dizziness
1998, J. Ayres [9]	5 yrs post AQF [86, 87] (AQF defined as a CFT titre of ≥1:256 or a 4-fold rise in phase II antibodies), no QFS definition, but rather description of complaints being significantly more prevalent in past QF cases i.c.w. controls: fatigue, sweating, breathlessness on exertion, blurred vision, with symptom severity in QF cases being higher for fatigue, blurred vision, sweating, memory deterioration, joint pains and headaches
1998, B. Bennet [45]	PIFS patients from DIOS or from the University Health Service at the University of New South Wales whose symptoms have been present ≤4 wks
1998, K. Kato [52]	Patients with chronic nonspecific symptoms, such as fatigue, joint aches, sleep disturbance, night sweats, myalgia affecting various muscle groups, nausea, persistent headache, and so on, without diagnosis or treatment history of QF and living in close contact with animals, presented between March 1996 and April 1997 to the Department of Internal Medicine and Psychosomatic Medicine, Nihon University Health Science Centre. Healthy controls: without/few complaints, who received annual examinations at the same hospital
1998, I. Penttila [19]	Definition QFS patients: 1) severe incapacitating fatigue ≥6 mo post AQF, with symptom score >100; 2) presence of myalgia and arthralgia; and 3) abnormal sweats, particularly at night. In addition, most patients had other symptoms such as inappropriate exhaustion on minor exertion, muscle fasciculation, headaches, bright light intolerance, ethanol intolerance, interrupted and unrefreshing sleep patterns, irrational irritability, loss of libido, depression, impairment mental concentration and short-term memory. Resolving QFS: recruited in similar way after several yrs observation, but symptom score dropped from values >100 to ≤95. QF without QFS: 6 mo post AQF without complex of symptoms and low symptom score (1-35)
1999, J. Scadding [26]	No study population or QFS definition
2000, R. Harris [20]	Definition of QFS patients: conform [19]. Controls: conform [19]
2002, J. Ayres [54]	10 yrs post laboratory-proven AQF [86, 87] (AQF defined as a CFT titre of ≥1:256 or a 4-fold rise in phase II antibodies). Controls: no serological evidence of past exposure to *C.b*. Definition fatigue: according to the 1994 international CFS criteria [15, 88]

S1 Table. Overview of study populations and used definitions (continued)

Included articles	Study populations and used definitions
2002, M. Wildman [7]	10 yrs post laboratory-proven AQF [86, 87] (AQF defined as a CFT titre of ≥1:256 or a 4-fold rise in phase II antibodies). Definition fatigue: score ≥4 using the traditional scoring system for the fatigue questionnaire [84]. Definition ICF: fatigued and describing fatigue >50% of the time for 6 mo. Definition CFS: ICF and functional impairment and ≥4 additional symptoms according to the 1994 international diagnostic criteria [15]. Controls: no serological evidence of past exposure to *C.b.*
2002, D. Raoult [38]	Definition QFS patient: residual asthenia following QF at 6 mo post AQF
2002, B. Marmion [33]	No study population or QFS definition
2002, M. Wildman [34]	No study population or QFS definition. Definition fatigue: according to the 1994 international CFS criteria [15, 88]
2003, T. Hatchette [3]	3 and 27 mo post AQF [89], no QFS definition. Controls: without AQF during same outbreak cohort
2003, K. Helbig [50]	Definition QFS patients: conform [19]. Recovered QFS: conform [19]
2003 K. Ikuta [55]	CFS based on the 1988 CDC working case definition [90] and the Ministry of Health and Welfare of Japan, from Tottori University Hospital, Yonago, and from Osaka University Hospital, Osaka, Japan. Healthy controls: from Tottori University Hospital Yonago
2004, Y. Arashima [6]	Definition QFS patients: prolonged nonspecific complaints, with general fatigue of unknown origin, or headache, slightly elevated body temperature (37-37,5˚C), arthralgia, or myalgia, with *C.b.* seropositive defined by IgMII ≥1:32 or IgGII ≥1:128 (or ≥1:64 if antibody for *B. henselae* was negative) and/or detectable *C.b.* DNA, for 3 mo till 4 yrs, between July and November 2001 from the Department of Internal Medicine of the Nihon University School of Medicine, Tokyo
2004, H. Thomas [56]	8 yrs post recruitment in 1991 from a random sample of farmers drawn from the Ministry of Agriculture, Fisheries and Food June Agricultural Census lists of agricultural holdings, with *C.b.* seropositivity defined by IgGII ≥1:32. No QFS definition
2005, B. Marmion [21]	Definition UK cases: 12 yrs post laboratory-proven AQF [86, 87] (AQF defined as a CFT titre of ≥1:256 or a 4-fold rise in phase II antibodies). Definition fatigue: conform [7]. Definition Australian QFS cases: conform [19, 20], 9 mo-5 yrs post AQF. Definition fatigue: according to the 1994 international CFS criteria [15]
2005, K. Helbig [51]	Definition QFS patients: as in [19, 21]. Definition AQF with asymptomatic recovery: 12 yrs post laboratory-proven AQF [86, 87] (AQF defined as a CFT titre of ≥1:256 or a 4-fold rise in phase II antibodies), with complete recovery without QFS or other chronic sequel. Definition QIE: clinical evidence of endocarditis by observation of vegetations on ultrascan or on histopathological examination of the diseased valve, and a compatible serological profile defined by IgGI and II >320, low or no IgM and IgAI ≥160, and PCR positive examination of valve vegetation specimens and in some instances by isolation of *C.b.* in cell culture or laboratory animals, Caucasians mainly from New South Wales and Queensland
2005, E. Iwakami [39]	Definition CFS patients: according to the 1994 international CFS criteria [15, 91], in combination with proven *C.b.* infection defined by IgG ≥1:128 (or ≥1:64 if *B. henselae* was negative), or IgM ≥1:32, and/or detectable *C.b.* DNA, for 8 mo till 11 yrs. Definition QFS patients: nonspecific complaints such as CF, slightly elevated body temperature, headache, arthralgia and myalgia of unknown origin for several mo or longer, but not meeting the 1994 international CFS criteria, in combination with a confirmed *C.b.* infection defined by IgG ≥1:128 (or ≥1:64 if *B. henselae* was negative), or IgM ≥1:32, and/or detectable *C.b.* DNA by n-PCR, regardless of the presence or absence of pre-existing infection, for 1 mo till 10 yrs

S1 Table. Overview of study populations and used definitions (continued)

Included articles	Study populations and used definitions
2006, I. Hickie [12]	Patients from DIOS with symptoms ≤6 weeks assessed at 3 and 6 wks, and 3 and 12 mo post AI, without pre-existing medical disorders or drug use likely to be associated with prolonged fatigue. Provisional PIFS: if SOMA scores at all time points up to and including 3 mo exceeded the established threshold score [92]. Confirmed PIFS: CFS at 6 mo post AI according to the 1994 international CFS criteria [15]. Controls: recovered promptly from the same infection
2007, D. Ledina [5]	Definition QFS patients: between January 2000 and December 2004 at Split University Hospital, Croatia. 1) 12 mo post AQF complaints of morning fatigue, disrupted sleep, headache, prolonged fatigue >24 hours post exertion, muscle pain, persistent slightly elevated body temperature, without CQF, meeting the 1994 international CFS criteria [15]. 2) 2 mo post AQF no symptoms, than start neck pain with 6 mo post AQF start of fatigue, insomnia, headache, sweating, unrefreshing sleep, for 12 mo, meeting the 1994 international CFS criteria [15] with positive ELISA IgG 1.6 and IgA 1.4. 3) 4 mo post AQF start symptoms of fatigue, disrupted sleep, headaches, muscle and joint pain, for 7 mo, meeting the 1994 international CFS criteria [15], with positive ELISA IgG 2.4 and IgA 1.5
2007, U. Vollmer-Conna [18]	PIFS patients from DIOS assessed at 1, 2, 3, 6, and 12 mo post AI, with confirmed PIFS if symptoms persisted beyond 6 mo with a score of ≥3 at all time points on the empirically derived subscale SOMA, without alternative explanations for ongoing illness and meeting the 1994 international CFS criteria [15]
2009, B. Marmion [37]	Samples from 11 patients ≥12 yrs post laboratory-proven AQF [86, 87], of whom 1 patients had slightly elevated body temperature, late-stage QIE
2009, L. Zhang [48]	Definition CFS/ME: idiopathic CFS/ME according to the 1994 international CFS criteria [15], from Bristol, London, and New York, and CFS/ME from [93, 94]. Definition Q-CFS/ME: CFS/ME according to the 1994 international CFS criteria [15] triggered by laboratory documented QF, from Birmingham. Definition endogenous depression: fulfilled DSM-IV criteria, from Bristol and surrounding area. Definition healthy blood donors: from Dorset National Blood Service [95]. Excluded were psychiatric diseases, smoking previous yr, alcohol or drugs abuse, current use or ≤3 mo of antibiotics, steroids, cytotoxic drugs or antidepressant
2010, Y. Kadota [46]	PIFS patients from DIOS or from a tertiary referral assessment clinic at a public teaching hospital in Sydney, and patients' current symptom profiles had to fulfill the 1994 international CFS criteria [15]
2010, O. Sukocheva [36]	Samples from patients 12 yrs post laboratory-proven AQF [86, 87], classification of patients into clinical groupings according to asymptomatic recovery or presence of QFS with or without other co-morbidity [7, 96], with a chosen subset from 1) recGr3, AQF with asymptomatic recovery; 2) QFSGr5, AQF followed by QFS without co-morbidity; 3) QFSGr6, AQF followed by QFS with fatigue-associated co-morbidity
2010, G. Limonard [58]	12 mo post laboratory-proven AQF (AQF defined as any inhabitant of the outbreak cluster area who presented with compatible clinical symptoms and a positive IFA serology, with an IgMII and IgGII ≥1:64 or seroconversion with 4-fold rise in antibody titre during FU). Controls: from neighbourhood of QF patient without QF history, with negative QF serology
2010, G. Limonard [57]	Post laboratory-proven AQF (AQF defined as any inhabitant of the outbreak cluster area who presented with ≥1 compatible clinical symptoms (fever, fatigue, chills, headache, myalgia, sweats, cough) and the demonstration of *C.b.* infection, as evidence by: 1) seroconversion or 4-fold rise in antibody titre using CFT in samples taken ≥14 days apart; 2) presence of IFA IgMII and IgGII ≥1:64; or 3) a positive serum PCR) assessed at baseline, 3, 6, 12 mo. Definition CQF: any inhabitant of outbreak cluster area with clinical entity compatible with endocarditis, vascular infection, osteoarticular infection, chronic hepatitis, or pregnancy, with an IgGI ≥800, for ≥6 mo post AQF
2011, G. Morroy [59]	12-26 mo post AQF (AQF according to the Dutch notification criteria [97] defined as a laboratory confirmation of QF with a seroconversion or a 4-fold rise in antibody titre between 2 subsequent tests with 2-4 wks time interval using CFT or IFA, and clinical presentation of fever, pneumonia or hepatitis, ≥18 yrs, notified in 2007/2008. Excluded: unknown onset of QF infection, incomplete questionnaires and questionnaires completed by another person

S1 Table. Overview of study populations and used definitions (continued)

Included articles	Study populations and used definitions
2011, H. van Woerden [69]	6 yrs post AQF (AQF defined as those who had clinical symptoms and serological evidence of AQF as demonstrated by an IgMII ≥80, or a fourfold rise on sequential CFT in 2002). Definition controls: who worked in the same factory but had no symptoms of AQF and no serological evidence of infection with no IgM, no CFT and no IgGI or IgGII at the time of the outbreak
2011, S. Galbraith [47]	Caucasian PIFS patients from DIOS with unexplained illness persisting ≥6 mo with a score of ≥3 at all time points on the empirically derived subscale SOMA, without alternative explanations for ongoing illness and meeting the 1994 international CFS criteria [15]. Controls: recovered promptly from the same infection
2012, B. Piraino [60]	Caucasian adult PIFS patients from DIOS [12] assessed at baseline, 2-3 wks, 4-6 wks, followed by 3-mo interval until 12 mo post AI
2012, B. Strauss [61]	2 yrs post laboratory-proven AQF [98]. Controls: without registered indicator for QF infection, from same general practitioners as study patients
2012, G. Morroy [62]	12-26 mo post AQF (AQF according to the Dutch notification criteria [97] defined as a laboratory confirmation of QF and clinical presentation with fever, pneumonia or hepatitis, notified in 2007/2008)
2012, Y. Arashima [28]	Definition QFS patient: 3 mo post AI with general fatigue, slightly elevated body temperature (37˚C or higher), cough, night sweats, arthralgia, noise in his ears, taste disturbance, and headache, without abnormalities in physical examination, laboratory examination including cultures and additional tests (X-rays, abdominal ultrasound, echocardiography, treadmill exercise test), but with positive n-PCR for *C.b.,* IgGII 1:64
2012, D. Raoult [27]	No study population or QFS definition
2012, H. Hussain-Yusuf [49]	Patients 6 yrs post serological evidence of AQF in 2002 [99]. Controls: worked in the same factory but were serologically negative for QF at the time of the outbreak
2012, J. Oosterheert [10]	No study population or QFS definition
2012, S. Yakubo [29]	Definition QFS patients: general fatigue, nausea, stomach pain, abnormal sensation in the mouth, sore throat, and trouble sleeping, with IgGI 1:256
2013, S. Keijmel [42]	Definition QFS patients: according to the Dutch guideline on QFS [17], referred to Radboud university medical center, Nijmegen, the Netherlands; adults (non-pregnant, non-lactating), ≥18 yrs, with laboratory-proven AQF since 2007 and/or positive serology fitting a past infection with *C.b.*, and being severely fatigued (CIS fatigue ≥35) for ≥6 mo, and being disabled because of fatigue (SIP total score ≥450), with a reference to AQF and absence of fatigue before the episode of AQF or a significant increase ever since. Excluded: CQF [100], AQF in the presence of risk factors for developing CQF necessitating prophylactic use of doxycycline, pregnancy or unwillingness to use effective contraceptives during the study, imminent death, inability to give informed consent, allergy or intolerance to doxycycline, somatic or psychiatric illness explaining chronic fatigue, current enrolment in other investigational drug trials or receiving investigational agents, receiving or having received AB >4 wks potentially active against *C.b.*, use of barbiturates, phenytoin, or carbamazepine, moderate or severe liver disease, current engagement in legal procedure for financial benefits
2013, S. Yakubo [41]	Definition QFS patient: 6 yrs post AI with general malaise, spasm left hand, slightly elevated body temperature, without abnormalities in physical examination, laboratory examination including pharyngeal culture and additional tests (chest X-ray, X-ray of larynx/pharynx/ears and paranasal sinuses, ECG, abdominal ultrasound, brain CT, EEG), with negative n-PCR for *C.b.*, IgMI and IgMII <1:16, IgGI <1:16, IgGII 1:32. Six mo after presentation IgGI 1:128
2013, M. van Asseldonk [32]	All notified, hospitalised, deceased and non-reported cases of QF, determined from [2] and [101]
2013, J. van Loenhout [25]	12 mo post AQF, patients ≥18 yrs diagnosed with QF in 2010 and 2011, who fulfilled the Dutch notification criteria for QF [102] were eligible for participation

S1 Table. Overview of study populations and used definitions (continued)

Included articles	Study populations and used definitions
2013, S. Yakubo [40]	Definition QFS patient: 2 mo post AI with severe fatigue, general malaise, arthralgia, myalgia, persistent slightly elevated body temperature (around 37˚C), whole-body lassitude, without abnormalities in physical examination, laboratory examination including a pharyngeal culture and additional tests (chest X-ray, ECG), but with positive n-PCR for *C.b.*, without positive antibodies
2013, R. Brooke [31]	QF notified patients with onset symptoms between 1 January 2009 and 31 December 2013. A(H1N1) pdm09 notified patients, reflected by influenza-like-illness registration from the Dutch Sentinel General Practice Network for influenza-like-illness from NIVEL Netherlands Institute for Health Services Research between 27 April 2009 and 26 April 2010
2013, Y. Arashima [30]	Definition QFS patients: 18 mo post AI with general fatigue, cough, dyspnoea, sputum, breathing difficulty, slightly elevated body temperature, headache, poor appetite, copious sweating, night sweating, nausea, vomiting, palpitations, and dizziness, without abnormalities on physical examination, laboratory examination (besides slight liver dysfunction), but with positive n-PCR for *C.b.*, IgMII 1:16, IgGII 1:128
2014, M. Kremers [63]	Post laboratory-proven AQF (AQF according to the Dutch notification criteria [97] defined as symptomatic patients with positive PCR for *C.b.* DNA in serum samples before the development of an IgMII antibody response measured by IFA or ELISA), between April 2009 and August 2009, and assessment 4 yrs post AQF, all who were still alive, ≥18 yrs and of whom a 12 mo FU sample was present
2014, J. van Loenhout [11]	Definition QF study population [103]: notified patients 1 yr post AQF in 2010 and 2011 (AQF according to the Dutch notification criteria defined as a laboratory confirmation of QF with a seroconversion or a 4-fold rise in IgG antibody titre in a paired serum sample with ≥2 wks time interval using CFT or IFA, presence of IgMII antibodies, positive PCR or culture in blood or respiratory material, presence of phase I antibodies, combined with a clinical presentation with fever, pneumonia or hepatitis, an onset of illness within previous 90 days [102], and ≥18 yrs. Definition Legionnaires disease study population: notified patients, 1 yr post Legionnaires' disease in 2010 (Legionnaires' disease according to the Dutch notification criteria defined as matching clinical symptoms, usually pneumonia, confirmed by at least 1 but preferably 2 of the laboratory diagnostic test: isolation of Legionella-species from respiratory secretions or blood; Legionella pneumophila-antigen in urine by radio-immuno-assay, ELISA, or immuno-chromatographic assay; Legionella-species by PCR in clinical material; significant titre of IgM by ELISA; significant titre elevation of antibodies. Healthy controls: via advertisements in local newspapers in the city of Nijmegen area. Excluded controls: underlying respiratory illness
2014, A. van Dam [64]	10-19 mo post LRTI as diagnosed by general practitioner between 1 May 2009 and 30 September 2009 in provinces of Northern Brabant and Gelderland, categorized into following ICPC groups: acute bronchitis, influenza, pneumonia, and other LRTI who were initially tested for QF, ≥18 yrs and ≤75 yrs. Definition QF positive: LRTI patients with positive diagnostic tests by either PCR, IFA, or CFT
2015, J. van Loenhout [67]	Over a period of 24 mo (assessed at 3, 6, 9, 12, 18 and 24 mo) post laboratory-proven AQF in 2010 and 2011 (AQF according to the Dutch notification criteria [102]), ≥18 yrs
2015, J. van Loenhout [65]	Definition notified QF patients: 4 yrs post laboratory-proven AQF in 2007 and 2008 (AQF according to the EU case definition [104] with laboratory criteria (isolation of *C.b.* from clinical specimen; detection of *C.b.* nucleid acid in clinical specimen; *C.b.* specific antibody response (IgGII or IgMII)), epidemiological criteria (exposure to common source; animal to human transmission), and clinical criteria (fever, pneumonia and/or hepatitis), onset of disease <90 days, ≥18 yrs. Definition non-notified QF patients: 4 yrs post laboratory-proven QF in 2008 and 2009 (according to the EU case definition, but only fulfilling the laboratory criteria and not the clinical criteria of fever, pneumonia or hepatitis), onset of disease <90 days, ≥18 yrs
2015, J. van Loenhout [66]	Definition QF study population [103]: notified patients assessed 3, 6, 9 and 12 mo post laboratory-proven AQF in 2010 and 2011 (AQF according to the Dutch notification criteria), ≥18 yrs. Definition Legionnaires disease study population [103]: notified patients 12 mo post Legionnaires' disease in 2010 (Legionnaires' disease according to the Dutch notification criteria)

Abbreviations: AI= Acute infection, AQF= Acute Q-fever, *B. henselae= Bartonella henselae*, *C.b.= Coxiella burnetii,* CDC= Centres for Disease Control and Prevention, CF= Chronic fatigue, CFS(/ME)= Chronic fatigue syndrome (/myeloencephalitis), CFT= Complement fixation test, CIS= Checklist Individual Strength, CNE= Culture negative endocarditis, CQF= Chronic

Q-fever, DIOS= Dubbo Infection Outcomes Study**,** cohort study of subjects ≥16 yrs followed from the onset of a confirmed and documented AI due to EBV; *C.b.*; or RRV ≤6 wks post AI until complete recovery, DSM-IV= Diagnostic Statistical Manual of Mental Disorders, EBV= *Epstein-Barr virus*, ECG= Electrocardiography, ELISA= enzyme-linked immunfluorsorbent assay, EU= European Union, FU= Follow-up, FUO= Fever of unknown origin, I.c.w.= In comparison with, ICF= Idiopathic chronic fatigue, ICPC= International classification of primary care, IFA= Immunofluorescence assay, IgA= Anti-phase IgA, IgG= Anti-phase IgG, IgGI= Anti-phase IgG I titre, IgGII= Anti-phase IgG II titre, IgM= Anti-phase IgM, IgMI= Anti-phase IgM I titre, IgMII= Anti-phase IgM II titre, LRTI= Lower respiratory tract infection, Mo= Month(s), (n-)PCR= (nested-) Polymerase chain reaction, PIF(S)= Post-infective fatigue (syndrome), Q-CFS(/ME)= Q-fever induced chronic fatigue syndrome (/myeloencephalitis), QF= Q-fever, QF(F)S= Q-fever fatigue syndrome, or Post-Q-fever chronic fatigue syndrome, or Post-Q-fever debility syndrome, or PQFS= Post-(acute)Q-fever (fatigue) syndrome, (Q)IE= (Q-fever induced) Infective endocarditis, Ref= Reference, RRV= *Ross River virus*, SIP= Sickness Impact Profile, SOMA= Empirically derived subscale of the SPHERE, used to record PIFS or illness duration. This reliably predicts disability and reflects patients' and doctors' reports of reasons for presentation to primary care. Scores ≥3 represents a clinically-significant fatigue state, UK= United Kingdom, Wks= Weeks, Yr(s)= Year(s)

S2 Table. Domain diagnosis

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
1999, J. Scadding [26]	Country unknown, 1999. Duration study NA	PO, comment on [19]	No patients/controls. Characteristics and co-morbidity: NR	NA	NA
2012, D. Raoult [27]	France, 2012	PO, comment on [100]	No patients/controls. Characteristics and co-morbidity: NR. Focus on CQF	NA	NA
2012, J. Ooster-heert [10]	Netherlands, 2012	PO, comment on [105]	No patients/controls. Characteristics and co-morbidity: NR. Focus on terminology of fatigue following QF	NA	NA
2013, J. van Loen-hout [25]	Netherlands, 2011-2012, single mea-surement 12 mo post illness onset	CoS	309 AQF patients, no controls. To assess use of NCSI and SF-36 in providing a detailed assessment of health status of QF patients and to evaluate which subdomains measure unique aspects of health status	NCSI, SF-36	NA

**** Definition of used study population in articles explained in a different table, including definitions of QFS and/or fatigue is applicable. Main information is on diagnosis. Some articles also contain relevant information on other domains: A= Aetiology, B/D= Background/descriptive, P/T= Prevention/therapy***

Abbreviations: AI= Acute infection, AQF= Acute Q-fever, CF= Chronic fatigue, CFS= Chronic fatigue syndrome, CoS= Cohort study, CQF= Chronic Q-fever, Mo= Month(s), NA= Not applicable, NCSI= Nijmegen clinical screening instrument, originally developed to provide a detailed assessment of health status of COPD patients. It combines a number of existing health status questionnaires, NOS= Newcastle–Ottawa Scale: S= selection (maximum of 4 stars), C= comparability (maximum of 2 stars), O= outcome (maximum of 3 stars); ★: star earned; ☆: item not applicable, NR= Not reported, PIF(S)= Post-infective fatigue (syndrome), PO= Personal opinion, PQFS= Post-(acute)Q-fever (fatigue) syndrome, QA= Quality assessment, QF= Q-fever, QF(F)S= Q-fever fatigue syndrome, Ref= Reference, SF-36= The Short Form (36) Health Survey, a patient-reported survey of patient health to assess quality of life of patients, functional impairment and reduced health related quality of life, Yr(s)= Year(s)

Outcome	Conclusions/recommendations	Other domain	QA (NOS) S	C	O
CFS, defined in clinical-descriptive terms, should convey no causal implication; when there is convincing evidence of a causal factor, the case belongs to a causally-defined subset of this syndrome. PQFS conforms to this desideratum	If mechanisms of complaints and specific therapeutic approaches are unknown, the term PQFS/QFS should be used as this leaves no doubt that findings are relevant to a CFS subset	NA	NA		
NA	CF is a non-specific subjective state, not a specific symptom of QF; no treatment is currently effective, it is not a diagnostic problem. Some patients with fatigue have high antibody titres, others not	NA	NA		
NA	Important to underline and recognise PIFS. New terminology QFS not useful; PIF described for many infectious diseases; not causative micro-organism, but disease severity correlates with symptom duration post AI. Can lead to cultivation, attracting patients with other intentions then getting better, ↑ healthcare costs	NA	NA		
NCSI: ↓ intercorrelations subdomains. 4 subdomains showed conceptual similarity (Subjective Pulmonary Symptoms, Subjective Impairment and Dyspnoea Emotions, and between Fatigue and Health Related Quality of Life) with ≥1 SF-36 subdomain (Vitality and General Health, and between Vitality and Mental Health and Social Functioning) and vice versa	Both NCSI and SF-36 can be used to measure health status in QF patients. Combining NCSI and 4 SF-36 subdomains (Role Physical, Bodily Pain, Social Functioning, Role Emotional), is preferred to obtain a detailed overview	NA	★★ ☆ ☆	☆ ☆	★ ☆★

S3 Table. Domain background/descriptive

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
1960, O. Powell [68]	Australia, 1958 July-1959 June	Observational pros. CoS	AQF patients (n=72, all ♂), describe clinical features and FU	NR	NA
1990, S. Reilly [53]	UK, 1972-1988, study period 16 yrs	Observational pros. CoS	Seroprevalence *C.b.* assessed after testing all FUO, respiratory infections, CNE, and hepatitis cases. Co-morbidity: NR. Time baseline (AQF) to measurement complaints NR	CFT, IFA (selected cases)	NA
1995, P. Harvey-Sutton [35]	Australia, yr NR	POB	N unknown. PQDS or PQCFS. No control group	NA	NA
1996, B. Marmion [8]	Australia, 1995. Study period: 5-14 yrs post AQF in 1981-89	CC	Post AQF laboratory proven (n=39) with QFS, skin-test /antibody negative vaccinated (n=39), skin-test or antibody positive without QF history (39), seronegative (n=39). Controls matched (sex, ≤10 yrs age). Co-morbidity: NR	54-item questionnaire based on symptoms	NA
1996, J. Ayres [14]	UK, 1995. Study period 6 yrs post AQF	CC	QF patients (n=83, 70 ♂) vs. matched (age, sex) controls (n=26). Co-morbidity: NR. Assess prevalence chronic symptoms 6 yrs post AQF	Questionnaire as in [8]	NA
1998, J. Ayres [9]	UK, 1994. Study period: 5 yrs post AQF	CC	71 symptomatic *C.b.* (mean age 55, 81.7% ♂, 32.4% current smokers). Matched (sex, age, ethnicity) controls: 142 (55 yrs, 81.7% ♂, 16.9% no febrile illness needing medical attention April-July 1989). Asses CFS symptoms prevalence post AQF	Modified questionnaire [8], including VAS per symptom	NA
1998, K. Kato [52]	Japan, March 1996-April 1997. Period: NA. Single blood samples	CC	52 patients (13 ♂, mean age 41 SD15, range 9-74): fatigue 77%, feeling feverish 44%, joint aches/myalgia 70%, headache 56%, cough/sore throat 42%; duration 4.9 yrs SD1.0, range 0.5-22. 52 healthy controls (35 ♂, mean age 52, SD10, range 38-82), and 70 cord blood samples	n-PCR	NA
2002, M. Wildman [7]	UK, 1999	CC	10 yrs post *C.b.* outbreak. 80 matched controls (sex, age, and smoking) random 2 local general practitioners (mean age 55.4, SD11.7, 68 ♂). 108 Q-exposed cases (mean age 55.6, SD11.8, 68 ♂) last contacted 1989/1994. Exclusion controls serology positive *C.b.* 77 matched pairs analysed. Aim: had subjects involved in West Midlands 1989 outbreak ↑ fatigue i.c.w. non-exposed controls 10 yrs later	11-item fatigue questionnaire, GHQ, CIS-R. MOS, SDQ. Laboratory test *C.b.*, spirometry, ECG, shuttle walk, incremental exercise test	NA

Outcome	Conclusions/recommendations	Other domain	QA (CR or NOS) S	C	O
Proportion of cases convalescence prolonged, with undue fatigue, setback up on moderate exertion, poor appetite, and occasional headache. 15/61 returned to work >6 wks post AQF, 12 >8wks. Mean period off work: 0-29 yrs 29 days, 30-49 yrs 45 days, 50-69 yrs 68 days. Total amount of time on workers' compensation payment 2013 days	Confirms previous observations that convalescence is more protracted in elderly	NA	★ ★ ★		
103 *C.b.* infections: 46 AQF, 5 CQF, 52 past infections. Details 61 cases (46 AQF, 5 CQF, 10 past infections). Outcome AQF: 57% uncomplicated, 4% prolonged fatigue (duration unknown), 11% underlying malignancy, 9% neurological sequelae, 9% persistent chest symptoms, 9% hepatic dysfunction. Outcome previous infection: 10% prolonged fatigue, 10% depression, 10% lymphadenopathy, 20% sarcoidosis, 10% polyarthritis nodosa	QF remains unpredictable, with a propensity to follow a protracted course. Prolonged serological and clinical surveillance of all QF cases is suggested	NA	★ ☆ ★		★ ★
Observation of bradycardia in PQDS patients	Bradycardia may be a sign of PQDS	NA	NA		
Combinations fatigue, night sweats, myalgia, fasciculation, with various minor symptoms more common in post AQF group, in 18-48% depending on number and mix of symptoms used for QFS definition. Met CFS CDC criteria: 11/39 post AQF, 0/39 vaccinees, 0/39 other controls	Interpretations range from compensation-driven through psychogenic perpetuation of original symptoms/depression, to chronic immune stimulation. Hypothesis persistence *C.b./*its antigens causes dysregulation macrophage/T-lymphocyte axis with aberrant monokine and lymphokine production mediating symptoms	Diag, A	★ ★ ★	★ ★	★ ★
QF group: 66% fatigue, 69% joint aches, 65% sleep disturbance, 59% cough, 53% sweats, irritability 54%, chest pain 51%, breathlessness 49%, headaches 47%, dizziness 39%, blurred vision 34%, alcohol intolerance 33%. ↑ Prevalence cases i.c.w. controls: joint pains, sleep disturbance, cough, sweats, irritability, chest pain, breathlessness, dizziness. No difference prevalence fatigue, blurred vision, headaches, alcohol intolerance	Findings support view that chronic PQFS exists which is in many ways similar to CFS	NA	★ ★ ★	★ ★	★ ☆
QF symptom prevalence: significant ↑ fatigue, sweating, blurred vision, breathlessness on exertion (especially non-smokers) than controls. QF cases symptom severity: ↑ fatigue, blurred vision, sweating, memory ↓, joint pains and headaches. 42.3% QF cases and 26% controls had CFS according to CDC criteria (p=0.025, post-hoc)	A syndrome characterized by undue fatigue, breathlessness on exertion, excessive sweating and blurred vision post *C.b.* infection, persists yrs. Defining questionnaire based syndrome due to QF is dangerous, objective measures needed. Mechanism elusive, subclinical cardiomyopathy/ autonomic dysfunction suggested	NA	★ ★ ★ ★	★ ★	★
Physical examination. CFS: 17/52 *C.b.* positive, amplification 438-bp fragments n-PCR. 52 controls 5/52 and 2/70 cord blood samples positive n-PCR. Mean age patients positive n-PCR 42, SD14, range 9-67. Estimated duration fatigue 77%, feeling feverish 53%, joint aches/myalgia 70%, headache 41%, cough/sore throat 47% was 4.0 yrs SD1.2. Positive ratio patients nonspecific complaints ↑ i.c.w. healthy controls (p<0.05) and cord blood (p<0.001)	High prevalence *C.b.* infection adult patients with long term, nonspecific complaints i.c.w. healthy controls, and possible existence chronic post AQF syndrome in Japan. Results appear to support the report of [8] and QFS concept	NA	★ ★		★ ★
108 Q-exposed, 64.8% fatigue, 34.3% ICF vs. controls 36.3% and 15.0%. 77 matched pairs: fatigue Q-exposed vs. controls: 64.9% vs. 35.1%, p<0.0001. ICF in 32.5% Q-exposed and 14.3% controls, p=0.01. 46.8% GHQ cases Q-exposed vs. 23.4% controls, p=0.004. Matched analysis: fatigue 66.7% Q-exposed, 34.7% controls, p<0.001, ICF 34.7% Q-exposed vs. 13.9% controls, p=0.004. CFS 19.4% Q-exposed vs. 4.2% controls. p=0.003. 47.2% Q-exposed had GHQ vs. 23.6% controls, p=0.004	*C.b.* cases exposed in 1989 had more fatigue than controls, some fulfilled CFS criteria. Uncertain if this is due to ongoing antigen persistence or to psychological effects of prolonged medical follow-up	A	★ ★ ★ ★	★ ★	★ ★

S3 Table. Domain background/descriptive (continued)

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
2002, B. Marmion [33]	Australia, 2002. Duration study NA	PO, comment on [38]	No patients/controls. Characteristics and co-morbidity: NR	NA	NA
2002, M. Wildman [34]	UK, 2002. Duration study NA	PO, comment on [38]	No patients/controls. Characteristics and co-morbidity: NR	CFS study group's 1994 CDC definition; 3 fatigue levels with ↑ seve-rity: (i) fatigue, (ii) idiopathic CF, and (iii) CFS	NA
2003, T. Hatchette [3]	Canada, yr study NR, study period: 1999-2001	CoS	Post AQF (n=33), controls without AQF during same outbreak cohort (n=24). Characteristics and co-morbidity NR. To follow effect of AQF on quality of life of patients 3 and 27 mo post AQF	Questionnaires on nature and duration of symptoms, SF-36	NA
2004, H. Thomas [56]	UK, 1999. Study period March-July 1999	CC	Random sample farmers (n= 425). Test seroprevalence *T. gondii* and *C.b.,* and association *T. gondii*, slow reaction and poor concentration, and between *C.b.* and persistent fatigue, and association organisms with depression/ depressive ideas. Duration infection unknown	CIS-R, venous blood	NA
2006, I. Hickie [12]	Australia, (sub study DIOS), yr study NR	CoS	N=253; 68 EBV (mean age 22, range 16-49, 57% ♀), 60 RRV (mean age 40, range 18-69, 45% ♀), 43 *C.b.* (mean age 40, range 16-73, 14% ♀), 82 not confirmed (mean age 38, range 16-77, 44% ♀). Control of fatigue: baseline, 3 and 6 wks, 3 and 12 mo post AI. Excluded; hypothyroidism/primary sleep-/psychiatric disorders. Controls (age and sex matched) recovered from AI at 6 mo	SPHERE, SOMA Laboratory and clinical examination	NA
2010, G. Limonard [58]	Netherlands, 2008	CC	54 post AQF patients (61.1% ♂, mean age 53.1, SD14.2, co-morbidity 40.7%, current smoker 44.4%). 23 seronegative neighbourhood controls (sex matched, age ±10 yrs) (42.3% ♂, mean age 53.6, SD9.7, co-morbidity 39.1%, current smoker 26.1). Asses health status 1 yr post AQF	NCSI	NA

Outcome	Conclusions/recommendations	Other domain	QA (CR or NOS) S	C	O
Previous report [20] did not claim persistent infection to cause PQFS. Substantial proportion AQF patients have QFS-like symptoms to QFS (milder version of acute phase symptoms without fever) for 6-9 mo post AQF and then recover. ±8-10% exhibit similar symptoms and do not reach immune/other homeostasis ≥1 yr	Systematic FU AQF patients needed, as 8-10% not recover ≥2 yrs post AQF	NA	NA		
Findings in fatigue prevalence study [7] differs from 5-10% found by others [38]. However, prevalence of fatigue in UK's general practice population is 38% vs. 36.3% in controls [7]. Idiopathic CF: 18.3% general practice vs. 15% in [7]	Lack explicit measurement instruments make comparison fatigue between studies impossible. Increased fatigue scores in QF exposed cohort were measured with standardized and well-validated instru-ments, permitting replication. Fatigue measurement is essential and should be standardized to compare studies	NA	NA		
3 mo post AQF only General Health scores of *C.b.* infected were ↓ than controls (p=0.03). 27 mo post AQF scores 5/8 domains and physical/mental summary scales ↓ i.c.w. controls. 27 mo post AQF 52% *C.b.* infected still reported symptoms, incl. 7 with initially resolved symptoms 3 mo post AQF. Of 3 *C.b.* infected symptoms resolved at 27 mo, who initially had persistent symptoms. ↓ scores General Health, Mental Health, Vitality and physical summary scales in those with persistent symptoms i.c.w. no symptoms. No initial symptoms nor antibiotic treatment of AQF predictive for developing persistent symptoms post AQF	Post *C.b.* infection symptoms can persist >2 yrs with significant quality of life impact. Data reflect further evidence of QFFS. Differences may reflect socioeconomic, physiological/ psychological effects of being labelled with QF rather than true post-infectious sequelae	A	★ ★ ★ ★		★ ★
15% relevant fatigue levels, 5% concentration problems, 5% depressive ideas, 4% depression, 6% general psychiatric morbidity. Seroprevalence: 45% *T. gondii*, ↑ with age, no gender differences; 31% *C.b.*, no association age/gender. 46 seropositive for both. Neither infection associated clinical relevant fatigue, concentration problems, depression, depressive ideas/overall psychiatric morbidity i.c.w. seronegative individuals, not associated ↑ risk psychiatric outcome after age and sex adjustment. ↑ % *C.b.* seronegative psychiatric symptoms i.c.w. seropositive	No evidence *T. gondii/C.b.* infections associated with neuropsychiatric morbidity, in particular poor concentration/fatigue	NA	★ ★ ★		★ ★
Provisional PIFS case rate 35% at 6 wks, 27% at 3 mo, 12% at 6 mo, and 9% at 12 mo, regardless of the infective agent, age, gender or psychiatric disorders. Confirmed PIFS: 28 cases (14 ♂, 14 ♀, mean age 37, range 17-63); 5 EBV, 3 QF, 13 RRV, 8 unconfirmed infections. I.c.w. all participant, no difference in age/sex. I.c.w. controls, comparable: premorbid psychiatric diagnosis, intercurrent psychiatric disorders. Confirmed PIFS: median score acute sickness factor rapidly ↓ to zero, for fatigue, musculoskeletal pain and neurocognitive disturbance remained ↑	Pro-inflammatory cytokines do not remain ↑ in PIFS. Key risk factor PIFS is severity acute illness; not demographic, psychological (premorbid/ intercurrent psychiatric disorders) factors	A	★ ★★ ★	★ ★	★
C.b. cases scored 1 yr post AQF significantly worse for all subdomains of symptoms. 52% cases clinically significant fatigue vs. 26% controls. Abnormal fatigue score QF patients 74% vs. controls 48%. Severe levels resp. 52% vs. 26%. NCSI scores of 11 seropositive and 23 seronegative controls not different for 8 subdomains health status	Sustained ↓ in health status 1 yr post AQF. NCSI scores from seropositive controls without clinical QF history comparable with seronegative controls, suggesting that clinical expression of AQF is essential in subsequent sustained ↓ health status	A	★ ★ ★ ★	★ ★	★ ★

S3 Table. Domain background/descriptive (continued)

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
2010, G. Limonard [57]	Netherlands, yr study NR. Study period 2007-2008	CoS	85 AQF patients (62% ♂, mean age 49 (18-80)). No controls. Co-morbidity: n=26 (6 cardiovascular, 3 pulmonary, 1 neurological, 4 rheumatological, 1 haematological, 3 depression, 5 diabetes, 3 other). Hospitalisation: 24 AQF patients	Post AQF: history, physical examination (6, 12 mo), IFA, CFT (baseline, 3, 6, 12 mo). Single transthoracic echocardiography	NA
2011, G. Morroy [59]	Netherlands, study period 2008-2011	CC	515 notified QF patients (2007 and 2008) with known 1st day of illness (mean age 50.4 and 51.8 yrs, 60% ♂, 57.2 % co-morbidity) vs. healthy individuals (n=65) and severe COPD patients (n=128) assessed 12-26 mo post AQF	NCSI	NA
2011, HC van Woerden [69]	UK, yr study 2008	Nested-CC	32 post AQF 6 yrs post outbreak Newport Wales, 2002 (mean age 50.18, SD 9.85). 13 controls (mean age 53.57, SD 8.86). Assess if i) CF ii) depression, and iii) ↓ physical functioning were more common in AQF patients 2002 i.c.w. controls	*C.b.* IFA, PHQ-9, Chalder Fatigue scale, GHQ	NA
2012, B. Strauss [61]	Germany, yr study NR	CC	84 post *C.b.* 2 yrs post Jena outbreak 2005 (mean age 48.4, SD15.2, ♀ 49%). 85 controls (mean age 49.3, SD16.8, ♀ 61% same general practitioner not controlled *C.b.)*. To investigate if fatigue/CF and/or CFS more frequent in *C.b.* infected vs. non-infected controls, and contrast QF patients with / without fatigue symptoms related to somatoform symptoms, hypochondrial worries/beliefs, psychosocial complaints and social support	MFI 20, SF-12, CDC-SI, SOMS, WI, OQ-45, F-Sozu K14, mini-DIPS	NA
2012, G. Morroy [62]	Netherlands, yr study: 2008-2011, duration: 2007-2010	CoS	515 notified AQF, known 1st day of illness in 2007 or 2008 (mean age resp. 50.4 and 51.8; 60% ♂, 57.2% with co-morbidity) FU 12 or 26 mo post AQF. Quantification of sick leave post AQF and long-term symptoms	NCSI and open questions regarding work	NA
2012, Y. Arashima [28]	Japan, yr study NR	CR	♂ 46 yrs, general fatigue, slightly elevated body temperature, night sweats, noise in ears, taste disturbance, headache, cough. Result: depressed with thoughts of death. Disease period 3 mo earlier. Co-morbidity: high-level depression (SDS 65) after start symptoms. PS 6. IgMI, IgMII, and IgGI negative, IgGII 1:64, n-PCR serum positive	PS, SDS, n-PCR, IFA	Minocycline 1 mo 200 mg/d, switched to 100mg/d (to-tal 3 mo). Antidepres-sant p.o.

Outcome	Conclusions/recommendations	Other domain	QA (CR or NOS) S	C	O
Post AQF 59% persistent symptoms at 6 mo and 30% at 12 mo FU. Self-reported fatigue initially 69%, at 6 mo 52%, at 12 mo 26%. No CQF. 59% had cardiac valvulopathy. ↑ antibody titres up to 3 mo, and ↓ in the following 9 mo	Screening echocardiography is no longer standard post AQF. At 6 mo fatigue is the most common complaint. Further studies needed with a control group to assess health status	NA	★ ☆★ ★	☆☆	★ ★
Abnormal fatigue score 58.9% QF patients, of which 43.5% severe. Similar scores for participants older and younger than 50 yrs. I.c.w. healthy controls (12.3% fatigue) QF patients scored significantly worse but better than COPD controls for subdomain fatigue. Hospitalisation, heart and lung disease, arthritis and depression significantly influence degree of fatigue	Sustained ↓ in health status 12-26 mo post AQF regardless of age. Policy makers ought to take this into account when considering measures to curb the extensive outbreak. Hospitalisation and co-morbidity predictors ↓ health status. More attention needed prevention and treatment long-term consequences	A	★ ★ ★	★ ★	★ ★
Chalder Fatigue scores cases significantly ↑ (P=0.047). PHQ-9 and GHQ scores equal i.c.w. controls. CS analysis relationship IgGII in 2008 and Chalder Fatigue scores (P=0.004) and PHQ-9 scores (0.049). Longitudinal association AQF and CF 6 yrs later. CS analysis relationship depression scores (PHQ-9) and positive QF serology	CF more common 6 yrs later in QF positive patients. Possible relationship ↑ *C.b.* IgGII, symptoms CF and depression. High antibody levels may indicate ↑ responder status rather than presence micro-organism. Points up the desirability trial antibiotic treatment in QFS	P/T	★ ★ ★ ★		★ ★
Post *C.b.* more fatigue symptoms and CF i.c.w. controls (54.8 vs. 20%, 32.1 vs. 4.7%). Not more CFS criteria (1 patient each group). *C.b.* with fatigue symptoms had significantly ↑ scores SOMS, WI, ↑ psychosocial complaints with OQ-45. Health Related Quality of Life QF group ↓ than controls	Fatigue symptoms common among QF patients. No ↑ CFS prevalence among QF patients. Combination fatigue and other psychosocial symptoms support biopsychological aetiology. CBT might be optional for prolonged fatigue post QF for those with psychological distress	A, P/T	★ ★ ★	★ ★	★
Post AQF 39.6% more 1 mo absent work. Hospitalisation during AQF, smoking and heart disease independent risk factors for long-term sick leave. At 12-26 mo post AQF 9.3% unable to function at pre QF levels due to fatigue and ↓ concentration. >30% not fully resumed daily activities; 80.8% due to fatigue, 4.9% due to respiratory problems. 12-26 mo post AQF 40% reported health complaints; fatigue 19.8%, difficulty concentrating 9.5%, muscle pain 9.0%, night sweats 7.9%, eye problems 3.8%	QF has considerable impact on productivity and perceived health status. Hospitalisation, indicator of AQF severity, was a predictor for long-term sick leave and fatigue	NA	★ ☆★	☆ ☆	★★
<1-2 weeks treatment, arthralgia and slightly elevated body temperature ↓, other symptoms improved. At completion, clinical symptoms almost resolved. IgMI, IgMII, IgGI, IgGII all negative, n-PCR negative. PS 1. SDS 47. 1 yr FU: no exacerbations	PQFS is associated with depression. Minocycline seems effective. Carefully monitor depression in PQFS	Diag, A, P/T	-/-, +, ++, ++, ++, NA, +/-,-/-		

S3 Table. Domain background/descriptive (continued)

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
2012, S. Yakubo [29]	Japan, yr study NR	CR	♂ 53 yrs, past QF infection, general fatigue, nausea, stomach pain, abnormal oral sensation, sore throat, trouble sleeping. Co-morbidity: depression	SDS	Antide-pres-sant, *C.b.* antibi-otic
2013, M. van As-seldonk [32]	Netherlands, 2012. Study period: 2007-2011	Economic evalua-tion	No patients/controls. Co-morbidity and characteristics: NR. Assess economic impact QF outbreak in the Netherlands, clarify costs-benefits control campaign, quantify and compare costs livestock sector, human health costs and disease burden. ±25% post AQF who seek medical attention expected to have CFS. Recovery period CFS 5-10 yrs (calculated with 7.5 yrs, working 50% contract time). Disability rate/weight factor: 0.14. 3.000 Euro/notified case	DALY (YLD, YLL). Deterministic socio-economic model	NA
2013, R. Brooke [31]	Netherlands, yr study NR. Study period Jan 2009-Apr 2010. Duration study NA	Burden of disease study	QF notifications Jan 2009-Dec 2009 (1407 ♂, 906 ♀) vs. influenza notifications Apr 2009-Apr 2010 (1219 ♂, 1508 ♀). Correction for underreporting QF (factor 12.6) and influenza (factor 4.4 to 5.6)	YLD, YLL (2009 Dutch life expectancy), DALYs, BCoDE comparison 2 infectious disease outbreaks	NA
2013, Y. Arashima [30]	Japan, yr study NR	CR	♀ 31 yrs, general fatigue, cough, dyspnoea, slightly elevated body temperature, headache, dizziness, poor appetite, copious sweating, night sweating, nausea, vomiting, palpitations. QFS (IgMII 1:16, IgGII 1:128, n-PCR positive) 18 mo post URTI, no result antibiotic treatment. Bronchial asthma 1 mo post URTI, 3 mo steroid inhaler, no improvement. Co-morbidity: moderate/greater depression (SDS 54). Suicide attempt	PS, SDS, n-PCR, IFA	Steroid inhaler 3 mo. Minocycline 200mg/d post diagno-sis QFS
2014, J. van Loen-hout [11]	Netherlands, yr study NR. Study period: 2011-2012, single measurement 12 mo post onset of illness	CC	QF patients (n=309, 53.7% ♂, mean age 49.9 (13.8), current smoker 28.8%, pre-existing health problems 40.6%, hospitalised 36.6%) vs. Legionella patients (n=190, 68.9% ♂, mean age 61.1 (11.5), current smoker 37.4%, pre-existing health problems 59.5%, hospitalised 61.1%), and QF group matched (age, gender) healthy controls (normal lung function, n=121, 55.4% ♂, mean age 51.4)). Assess and compare health status patients 1 yr post QF/Legionella	NCSI, SF-36	NA
2014, A. van Dam [64]	Netherlands, 2009-2011, inclusion 1st May-30th September 2009	CC	50 QF seropositive LRTI (mean age 48.1, SD14.3) vs. 32 QF seronegative LRTI patients (mean age 57.2, SD14.4); 18-75 yrs. Comparable gender (60% vs. 50% ♂), current smoking (40% vs. 30%), hospitalisation during LRTI (10% vs. 7%), co-morbidity (42% vs. 56%). QF positive: more often pneumonia i.c.w. QF negative. Assess if LRTI due to QF has higher health status impairment i.c.w. other LRTIs 15 mo post AI	NCSI (completion 10-19 mo post LRTI, mean 15 mo). QF positive tested with PCR, IFA or CFT	NA

Outcome	Conclusions/recommendations	Other domain	QA (CR or NOS) S	C	O
Depression triggered by *C.b.* led to suicide	Treat *C.b.* with antibiotic. Check for depression, if present treat aggressive. Consider psychiatrist early. SDS is useful in these cases	Diag P/T	-/-, +/-, +/-, +/-, +/-, NA-, -/-		
Total disease burden 2462 DALY, of which CFS 1481 DALY, CQF 806 DALY. Income losses accumulate over time due to long duration paid sick leave. Treatment costs: <2% total human health costs. Using extreme upper and lower bounds; CFS 30% of cases, duration ≥10 yrs, disability weight 0.20, 18.167 Euro/DALY; CFS in 20% of cases, duration ≥5 yrs, disability weight 0.10; 87.602 Euro/DALY	Most long-term benefits implemented control programme reduced disease burden and human health costs. Majority short-term intervention costs in dairy goat sector. Estimated: total loss in public sector: 222 Million Euro; total loss 307 Million Euro. Estimated burden human health 2462 DALY's 2007-2011. CFS most prominent burden	NA	16/19 checklist items positive **		
QF: 5797 DALYs, 1771 from acute illness, 4027 from sequelae. PIFS 57% total burden, mainly 45-49 age group. Influenza: 24484 DALYs, 3033 from sequelae. Total no DALYs due to influenza higher than QF, but on per case basis QF more severe. QF is 8.28x worse than influenza regarding composite health measures due to long-term sequelae up to 10 yrs post AI	Intervention prioritization for QF should target immediate interventions for containment and support of long-term sequelae. Long-term sequelae contribute a high burden of disease	NA	NA		
At least 3 mo minocycline: improvement generalized symptoms and bronchial asthma. PS 1. n-PCR negative. IgMII 1:16, IgGII 1:16. FU 9 mo post treatment: bronchial asthma and fatigue disappeared. Depression alleviated	*C.b.* can cause bronchial asthma and should be considered when resistant to standard treatment accompanied by slightly elevated body temperature or general fatigue. Be aware of suicide attempts	Diag, P/T	-/-, ++, ++, ++, ++, NA, +/-,-/-		
Worse score QF vs. Legionella patients on subdomains fatigue (60.2% vs. 50.0%, i.c.w. 2.5% healthy controls), General Quality of Life (50.0% vs. 42.6%), Role Physical. Adjustment confounders: only Role Physical remained different. In both QF and Legionella: proportion severely affected patients ↑ i.c.w. controls	Certain infectious illnesses are followed by long term impaired health status, including PICF. QF and Legionella patients are affected on ≥1 aspects health status, especially fatigue, General Quality of Life, Role Physical. Impact QF seems higher than from Legionella. Health staff need to be aware of this impact in order to provide adequate care	NA	★ ★ ★	★ ★	★
QF positive LRTI: severely affected General Quality of Life (40%) and fatigue (40%), QF negative LRTI: fatigue (64%) and subjective pulmonary symptoms (35%). 40% QF positive and 56% QF negative severely affected on >1 subdomain. No difference health status scores QF positive and QF negative LRTI patients for all subdomains except subjective pulmonary symptoms	Large group LRTI patients affected >1 aspect of health status 15 mo post LRTI. Little difference in health status QF positive and QF negative LRTI patients. General practitioners ought to be aware of long-term health problems in LRTI patients in general	NA	★ ★ ★ ★	★ ★	★ ★

S3 Table. Domain background/descriptive (continued)

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
2015, J. van Loen-hout [67]	Netherlands, study period: 2010-2013, FU at 3, 6, 9, 12, 18, and 24 mo post AQF	CoS	336 post AQF patients (in 2010-2011, 54.8% ♂, mean age 48.5, SD13.9, co-morbidity 39.7%), comparison NCSI scores matched (age, gender) healthy controls. To assess health status progression of QF patients over 24-mo period, and identify influencing factors	NCSI (3, 12, 18, and 24 mo), SF-36, questionnaires	NA
2015, J. van Loen-hout[65]	Netherlands, yr study 2011-2013, Single measurement 4 yrs post AQF	CC	448 notified post AQF (2007-2008, 57.6% ♂, mean age 54.4, SD12.4, co-morbidity 51.1%) vs. 193 symptomatic non-notified post QF (2008-2009, 45.1% ♂, mean age 50.2, SD15.3, co-morbidity 52.6%), vs. healthy controls. To compare long-term health status notified and non-notified QF patients	NCSI	NA
2015, J. van Loen-hout [66]	Netherlands, yr study NR. Study period: 2010-2012, FU 3, 6, 9 and 12 mo post AQF, 12 mo post AI Legionella	CoS, with partly CC	336 QF, 190 Legionella patients. Assess (progress of) work participation of QF patients up to 12 mo post AQF, identify associated factors, and compare work participation between QF and Legionella patients 12 mo post AI	Questionnaire 3, 6, 9 and 12 mo post AQF, ADIQ at 12 mo both groups	NA

Definition of used study population in articles explained in a different table, including definitions of QFS and/or fatigue is applicable. Main information in this table is on background/descriptive. Some articles also contain relevant information on other domains: Diag= Diagnosis, A= Aetiology, P/T= Prevention/therapy

***** Quality assessment economic evaluation study was assessed using the 'Evers checklist' [23]***

Abbreviations: ADIQ= Acceptance of Disease and Impairments Questionnaire, to assess the different stages of the grieving process due to the infection that patients underwent, AI= Acute infection, AQF= Acute Q-fever, BCoDE= Burden of Communicable Diseases in Europe project, attributes DALYs of an infectious disease to the year the acute infection occurs. This allows for the attribution of long-term sequelae, which may generate a higher number of DALYs, to the causative infection rather than only the initial acute illness, *C.b.= Coxiella burnetii,* CBT= Cognitive behavioural therapy, CC= Case-control study, CDC= Centres for Disease Control and Prevention, CDC-SI= German version of the CDC-Symptom Inventory. The inventory asks in detail for 11 symptoms that commonly accompany CFS. These symptoms have to be described with respect to their intensity and frequency related to the last months, CF= Chronic fatigue, CFS= Chronic fatigue syndrome, CFT= Complement fixation test, CIS-R=Revised Clinical Interview Schedule to assess the symptoms of neurotic psychopathology in the week prior to interview. The CIS-R is made up of 14 sections, each covering a particular area of neurotic symptoms. Summed scores from all 14 sections range from 0-57, the overall threshold for clinically significant psychiatric morbidity is 12, CNE= Culture negative endocarditis, CoS= Cohort study, CQF= Chronic Q-fever, CR= Case-report, CS= Cross-sectional, DALY= A composite health measure that represents one lost year of healthy life between the current health status and that of an ideal health situation. Calculated as the sum of YLD for incident cases and the YLL due to premature death, DIOS= Dubbo Infection Outcomes Study**,** cohort study of subjects ≥16 yrs followed from the onset of a confirmed and documented AI due to EBV; *C.b.*; or RRV ≤6 wks post AI until complete recovery, EBV= *Epstein-Barr virus*, ECG= Electrocardiography, F-Sozu K14= To assess social support, a 14-item questionnaire resulting in a total score describing the quality and quantity of a person's social support, FU= Follow-up, FUO= Fever of unknown origin, GHQ= General health questionnaire, 12-item questionnaire to detect current cases of psychiatric co-morbidity, I.c.w.= In comparison with, ICF= Idiopathic chronic fatigue, IFA= Immunofluorescence assay, IgGI= Anti-phase IgG I titre, IgGII= Anti-phase IgG II titre, IgMI= Anti-phase IgM I titre, IgMII= Anti-phase IgM II titre, LRTI= Lower respiratory tract infection, MFI 20= German version of the Multidimensional Fatigue Inventory, a commonly used 20-item questionnaire indicating different dimensions of fatigue, Mini-DIPS= Diagnostic interview, a short form of the diagnostic interview of psychological disorders, Mo= Month(s), MOS= Medical outcome study 20-item questionnaire, used to define functional impairment in the construction of the CFS definition, NA= Not applicable, NCSI= Nijmegen clinical screening instrument, originally developed to provide a detailed assessment of health

Outcome	Conclusions/recommendations	Other domain	QA (CR or NOS) S	C	O
Significant linear improvement over time in 9/12 health status subdomains. Severely affected: fatigue 73.0% at 3 mo, 60.0% at 12 mo, 37.0% at 24 mo (vs. 2.5% healthy reference group), General Quality of Life 42.2% at 3 mo, 50.2% at 12 mo, 33.7% at 24 mo (vs. 19.8% healthy reference group). For 3 most severely affected subdomains (fatigue, General Quality of Life, Role Physical): females, young adults, pre-existing health problems, at baseline were associated with ↓ long-term health status	Despite linear improvement over time, >1/3 patients had ↓ health status at 24 mo. Results suggest that psychological distress is not an important factor in explaining ↑ fatigue levels	A	★ ★	★ ★	★ ★
Notified: more ♂, ↑ age vs. non-notified. Equal proportions followed additional treatment for long-lasting health effects of QF, but addition antibiotic treatment slightly ↑ in notified patients. In both groups: fatigue (notified 50.5% vs. non-notified 54.6%) and quality of life (notified 42.3% vs. non-notified 44.4%) most severely affected subdomains. No difference long-term health status notified vs. non-notified, patients scored worse all subdomains i.c.w. healthy controls	Long-term health status is not determined by symptoms during acute QF. Little improvement health status between 1 and 4 yrs post AQF. Implication 2007-2009 Dutch QF outbreak underestimated if only considering notified patients. True burden of disease due to QF outbreak is larger	A	★ ★	★ ★	★
↓ Proportion QF patients with ↓ work participation, 45% at 3 mo to 19% at 12 mo (vs. 15% Legionella patients at 12 mo). Median proportion reduction hours worked stable over time. ↑ Proportion patients not reporting symptoms up to 12 mo. No symptoms at 12 mo: QF 44% vs. 57% Legionella. Most frequent symptoms at 12 mo QF: fatigue, concentration/memory problems, headache (all 24%), and muscle pain 23%. Legionella: concentration/ memory problems (21%), fatigue, respiratory pro-blems, joint pains (13%). Grieving process: QF ↑ score denial and resistance, ↓ acceptance i.c.w. Legionella. QF; associated factors ↓ work participation: symptoms, ↑ level sorrow, former smoker (i.c.w. never smoked), no alcohol consumption, following treatment for long-term health effects. Median time to full return to work in QF group <3 mo	Almost 1/5 QF patient and 1/6 Legionella patient ↓ work participation at 12 mo. Occupational and insurance physicians need to be aware of long-term impact of QF and Legionella on work participation. Suggestion; undergoing QF leads to grief process similar to progressive disease, underlining the severity of sequelae due to QF	NA	★ ★ ★ ★		★ ★

status of COPD patients. It combines a number of existing health status questionnaires, NOS= Newcastle–Ottawa Scale: S= selection (maximum of 4 stars), C= comparability (maximum of 2 stars), O= outcome (maximum of 3 stars); ★: star earned; ☆: item not applicable, N/No= Number (of), (n-)PCR= (nested-) Polymerase chain reaction, NR= Not reported, OQ-45= OQ-45, to measure psychological symptoms and general impairment. It is a common symptom inventory used in many psychotherapy studies to reflect total impairment, social as well as interpersonal distress and impairment of social role performance, PHQ-9= a self-administered subset of the PRIMA-MD diagnostic instrument for common mental disorders to assess symptoms severity of depression, PICF= Post-infectious chronic fatigue, PIF(S)= Post-infective fatigue (syndrome), P.o.= Oral, PO= Personal opinion, POB= Personal observation, PQCFS= Post-Q-fever chronic fatigue syndrome, PQDS= Post-Q-fever debility syndrome, PQFS= Post-(acute) Q-fever (fatigue) syndrome, Pros.= Prospective, PS= Performance status score (range 0-9), which reflects the grade of fatigue/malaise to assess the severity of CFS, QA-CR= Quality assessment; for CR no quality checklists are available. Therefore, the following eight criteria for quality assessment were determined; addressing an appropriate and clearly focused question, representative population, description of the survey method or data collection, outcome measures defined, outcome measures described, response rate reported and results valid and applicable to the patient group targeted. The articles scores on these items:-/-,-, +/-, +, or ++, based on the Coordination of Cancer Clinical Practice Guidelines in Europe criteria, QF= Q-fever, QF(F)S= Q-fever fatigue syndrome, Ref= Reference, RRV= *Ross River virus*, SD= Standard deviation, SDS= Self-rating depression scale, consisting of 20 questions, score per question: 1-4 points, SDQ= Somatic Discomfort Questionnaire, a checklist of 25 somatic symptoms, as somatic symptoms are important minor symptoms in the construction of CFS definition, SF-12= The Short Form (12) Health Survey, SF-36= The Short Form (36) Health Survey, a patient-reported survey of patient health to assess quality of life of patients, functional impairment and reduced health related quality of life, SOMA= Empirically derived subscale of the SPHERE, used to record PIFS or illness duration. This reliably predicts disability and reflects patients' and doctors' reports of reasons for presentation to primary care. Scores ≥3 represents a clinically-significant fatigue state. Provisional PIFS: SOMA scores ≥3 at all time points up ≤3 months. Confirmed PIFS: symptoms persisted >6 months, and alternative explanations for ongoing illness was excluded, SOMS= Screening for Somatoform Disorders, a 53-item questionnaire assessing symptoms common for somatoform and somatisation disorder leading to the calculation of different indices, SPHERE= Somatic and Psychological Health Report, to assess a wide range of physical and psychological symptoms, including severity and duration of symptoms, *T. gondii= Toxoplasma gondii,* UK= United Kingdom, URTI= Upper respiratory tract infection, VAS= Visual analogue score, 10cm scale to quantify symptom severity, Wks= Weeks, WI= Whiteley Index, to measure the patients' tendency for hypochondriacal worries and beliefs, YLD= Number of years lost due to disability: number of incident cases x average duration of the disease x weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead), YLL= Years of Life Lost due to premature death; number of deaths caused by the disease x standard life expectancy at the age at which death occurs, Yr(s)= Year(s)

S4 Table. Domain aetiology

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
1998, B. Bennet [45]	Australia, yr study NR (sub study DIOS). Study period NR	Pros. CoS	17 EBV, 8 QF, 5 RRV (82% ♂, mean age 29 (15-77)). Explore longitudinal relationships between physical and psychological symptoms and immunological factors during peak illness (symptoms <4 wks before presentation) and recovery phase (2 and 4 wks after baseline) of AI (EBV, *C.b.*, and RRV)	Baseline: interview, POMS, GHQ, SOFA, CIDI, DTH skin response. At 2 wks: interview, POMS, GHQ, SOFA. At 4 wks: interview, POMS, GHQ, SOFA, DTH test	NA
1998, I. Penttila [19]	Australia, yr study NR. Single measure-ment study	CC	18 QFS patients (mean age 39 (33-45), symptom score >100, mean 145 (133-157)). 27 controls; 6 resolving QFS (symptom score <100, mean age 39 (31-48)), 5 past AQF (>6 mo) without QFS (symptom score 15 (1-35), mean age 39 (25-54)), 8 QF skin test- vaccinated (mean age 44 (31-56), symptom score 7 (1-13)), 8 QF- healthy controls (mean age 32 (23-40), symptom score 5 (1-9)). Mean age groups equal. Asses cytokine release patterns PBMC stimulated with QF (phase I and II), measles antigens and PHA, in 72-h culture	Interview; clinical history, presence, frequency, and intensity of 16 minor and major QFS symptoms scored on linear numerical scale 1-20. Analysis of: IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, IFNy, TNFa, TNFb and TGFB	NA
2000, R. Harris [20]	Australia, yr study NR. Study period NR. Mean period sampling 37 mo post AI (2 after 9 mo, remainder after ≥12)	CC	QFS (n=29); 18 from [19], 11 additional with QFS post AQF. PBMC (n=29), liver biopsy (n=14), BMA (n=20). Controls from [19]. PBMC: patients no QFS post AQF (n=5); post-vaccination (n=7), *C.b.* seronegative healthy controls without CFS (n=6). BMA (n=6) of patients with diseases other than QF. Positive PCR controls; QIE or recrudescent infection in pregnancy (n=10)	PCR (target IS1111a), several primer sets in conventional PCR and TaqMan PCR system	NA
2002, J. Ayres [54]	UK, 1999. Study period 10 yrs post AQF	Nested CC	N=85 *C.b.*-exposed (85.6% ♂, mean age 54.7, SD12.0, co-morbidity 29.4%) vs. n=75 matched (sex & smoking) QF seronegative controls (86.7% ♂, mean age 55.3, SD11.4, co-morbidity 29.3%). Determine if persistent fatigue post AQF represents sub-clinical cardiomyopathy	Questionnaires, 12-lead ECG, echocardiography, spirometry, shuttle walk distance, MUGA scan (only in subset)	NA

Outcome	Conclusions/recommendations	Other domain	QA (NOS) S	C	O
Baseline: fatigue and malaise most common symptoms. Depressive and anxiety symptoms not prominent. 46% cases no DTH skin response, indicative of impaired cell-mediated immunity. Over 4 wk period, improvement somatic and psychological symptoms, but 63% remained fatigue. Most symptoms improved; somatic changes notable in fatigue and malaise, rather than psychological (anxiety and depression). Psychological changes due to changes in perception fatigue and vigour. ↓ reported fatigue correlated with ↑ DTH skin response (indicating relation between fatigue and cell-mediated immunity) and GHQ scores	Fatigue commonly remains a prominent complaint at 4 wks. Resolution of fatigue is associated with improvement in cell-mediated immunity, supporting an immunological basis for PIF	NA	★ ★ ★ ★		★ ★
Aberrant cytokine release patterns of PBMC QFS patients stimulated with QF antigens; ↑ IL-6 release (mean 502 pg/ml, i.c.w. 47-53 pg/ml in other groups, p=0.018). Mean PBMC response of QFS to PHA ↑ than controls, not significant. 72% QFS patients: IL-6 release values >100 pg/ml; 66pg/ml max value for 95% CI of control groups. QFS ↓ IL-2 responders with QF antigens (p=0.014), but equal IL-2 release post PHA stimulation. QFS: ↑ IFNy responders (p=0.0008); no difference median [IFNy] released (p=0.14). IL-1 ↑ on PHA stimulation PBMC from QFS than controls (p=0.03), no difference with QF antigens. >IL-5 responders among QFS with QF antigens. Correlation IL-6 in conditioned medium, total symptom score, and scores other key symptoms. In QFS: persistent IL-6 upregulation, no time-correlation with AQF	Hypothesis: cytokine deregulation due to chronic immune stimulation and modulation by persistent *C.b.*/antigens. Aberrant IL-6 response not claimed to explain QFS pathogenesis. IL-6 might contribute to QFS symptomatology. QFS development appears to require cellular immune response against *C.b.* antigens. A speculative unifying concept is that QFS and QIE represent different poles of dysfunctional cell-mediated immunity response to *C.b.* QFS patients have positive LMR to QF antigens, greatly ↑ IL-6 release patterns from PBMC, IFNy upregulated, but IL-2 downregulated. Fatigue can be intermittent (relapsing) or continuous in QFS	Diag, B/D	★ ★ ★ ★	★	★ ★ ★
C.b. detection in QFS: PBMC 5/29, liver biopsy 2/14, BMA 13/20. In PBMC: no QFS 0/5, vaccinated 0/7, seronegative 0/6. In BMA: other diseases 0/6. PCR positive in QIE/placentitis 10/10	*C.b.* DNA in bone marrow 0.75-5 yrs post AQF infection unveils new QF pathology state. *C.b.* live/dead/other bio-entities not defined. Pattern suggestive paucibaccillary infection presumably under immune control, but not eliminated. Supports previous reports relationship QFS, cytokine dysregulation and immunomodulation from *C.b.* persistence. Bone marrow could be focus cryptic infection which might seed other sides. Before drawing conclusions on QFS, investigate bone marrow in more patients with/without QFS/other sequelae	Diag	★ ★ ★ ★		★ ★
68.2% *C.b.* cases fatigue any duration, 42.4% fatigue excluding co-morbidity. 20% CDC-defined CFS vs. 5.3% controls, 8.2% excluding co-morbidity vs. 0% controls. Normal ECG's 76.5% cases, 69.3% controls, no differences. Echocardiography: controls ↓ fractional shortening. Fatigued vs. non-fatigued QF cases: comparable echocardiography, ECG, shuttle walk distances, pack years smoking. Normal MUGA scan 6 *C.b.* cases (CDC-defined CFS without co-morbidity)	Findings do not support the existence of a sub-clinical cardiomyopathy in patients with fatigue after AQF, therefore not explaining breathlessness and fatigue. Chronic heart disease following AQF is rare and limited to IE	B/D	★ ★ ★	★ ★	★ ★ ★

S4 Table. Domain aetiology (continued)

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
2002, D. Raoult [38]	France, 2002. Duration study NA	PO	No patients/controls. Characteristics and co-morbidity: NR	NA	NA
2003, K. Helbig [50]	Australia, yr study NR. Single measurement study	CC	23 active/recovered QFS, 42 controls Red Cross blood donors, all Caucasians. To compare variability in phenotype distribution among range of cytokine and accessory immune response genes in PQFS and controls	Genotyping within NRAMP1 gene, HLA typing for HLA-DR and HLA-B; 25 polymorphic variants 14 genes analysed	NA
2003, K. Ikuta [55]	Japan, yr study NR. Single measurement study	CC	44 CFS (H1: 22 CFS, 14 ♂, 23-61 yrs; H2: 22 CFS, 17 ♂, 20-46 yrs), 38 healthy controls (20 ♂, 20-59 yrs). To investigate association viral infections with CFS and 2-5AS activity in PBMC in Japan in 2 hospitals (H1, H2) different areas	*C.b.,* IFA IgGII positive titre ≥1:64	NA
2005, B. Marmion [21]	Australia and UK, 2001, study period NR	CC (case follow-up study)	*C.b.* positive UK cases (n=92) 12 yr post AQF (Birmingham 1989, n=92 blood samples, n=91 PBMC, n=35 BMA), Australian cases (n=29) 9 mo-5 yrs post AQF (n=29 blood samples and PBMC, n=20 BMA, n=14 liver biopsy) with CFS (CDC-criteria). To compare prevalence infection markers between cohorts	I. *C.b.* PCR (directed against several targets in the genome) DNA detection PBMC and bone mar-row, II. CFT, IFA Phase I & II, III. isolation *C.b.* cell cultures of mice- PCR positive	NA
2005, K. Helbig [51]	Australia and UK, yr NR, study duration NR	CC (gene-tic asso-ciation)	31 QFS patients vs. uncomplicated recovery up to 12 yrs post AQF (n=22) vs. QIE (n=22, mean age 57, range 29-78, time lag infection-IE 8.8 yrs, SD12, range 2-40) i.c.w. standard control panels general population. To compare frequencies of allelic polymorphisms in immune response genes in different QF patient groups	Whole blood, DNA extraction, HLA typing, microsatellite typing, SNP analysis	NA
2007, U. Vollmer-Conna [18]	Australia, 1999 (sub study DIOS); 12 mo collection period. Appraisal 1, 2, 3, 6, 12 mo post AI	Pros. CoS	22 PIFS patients (11 EBV, 6 RRV, 5 *C.b.*) vs. 42 aged-matched controls who recovered <6 wks of EBV (n=17), RRV (n=14), and QF (n=11). Analysis influence PIFS status on symptom severity and cytokine production i.c.w. controls	SPHERE, BDQ. SOMA score ≥3 to record PIFS	NA

Outcome	Conclusions/recommendations	Other domain	QA (NOS) S	C	O
6 mo post AQF 5-10% residual asthenia, very few >1 yr. Subjective symptoms difficult to quantify. CF: difficult to define, with different prevalence. Unknown if CF psychological in origin/directly caused by bacterium. Might reflect observational bias, *C.b.* strain or cultural differences, or genetic susceptibility	Amplicon production PCR in peripheral blood CF patients needs confirmation. New tools might allow to examine aetiology incompletely understood diseases caused by intracellular bacteria	B/D	NA		
No significant variation frequency individual SNP patients and controls, but more variants differing from wild type in patients i.c.w. controls, p=0.025. Differences allelic frequencies HLA-DR, significant ↑ frequency HLA-DR11 in QFS, but not HLA-B. Phenotype frequencies SNP in genes not significantly different from controls. Variation allele distribution QFS and controls INFγ di-nucleotide repeat. IFNγ genes; ↑ prevalence homozygous state IFNγ allele 2 in intron 1 in QFS	Possible genetic role expression overt chronic manifestations, e.g. individual variation *C.b.* immune response. Given complexity of genetic control of immune system, a simple 1-to-1 relation between QFS expression/other chronic complication QF and a particular polymorphic variation in a cytokine or immune control gene is unlikely. Effects are more likely multigenic	Diag	★ ★ ★	★	★
2-5AS activity: 19 (mean 2.23) in H1, 7 (mean 0.91) in H2, 4 in controls (mean 0.74). Differences H1 and H2, and H1 and controls (p<0.01). No difference H2 and controls. IFNa similar in few CFS patients and controls. No relationship 2-5AS and IFNa positivity. EBV anti-EA-IgG antibodies in 9% and 32%in H1 and H2. IgG *C.b.* positive 6/22 H1, 0/22 H2, 1/9 controls. No difference *C.b.* positive H1 and controls/patients H2 and controls. No correlation 2-5AS activity and *C.b.* titres (p>0.05)	2-5AS activity ↑ PBMC CFS patients. CFS may be associated EBV/*C.b.* ↑ 2-5AS suggests immunological dysfunctions with virus infections in CFS. No relation titres *C.b.* and 2-5AS activities. 2-5AS activity changed from positive to negative in 1 CFS patient when *C.b.* antibodies disap-peared, suggests *C.b.* association 2-5AS activity some CFS patients. Imply 2-5AS in some CFS patients activated by other mechanisms, in addition to EBV and *C.b.*	NA	★ ★		★ ★
Both groups remained seropositive irrespective clinical state. *C.b.* genomic DNA detected by PCR in 65% of BMA from Australian vs. 88% Birmingham patients. No *C.b.* isolated from PCR positive samples	Results indicate more complex interaction between host-regulated, persistent carriage of *C.b.* and disease. An additional variable factor of host regulation of cellular immune response must determine levels of persistence and symptomatic outcomes. Hypothesis: in QF without sequelae, process largely confined to bone marrow. In QFS, modulation by the patient's immunogenetic background causes ↑ levels of *C.b.* genomes in bone marrow and ↑ shedding into peripheral blood	Diag	★ ★★ ☆		★★
Significant differences between 3 groups. QFS patients differed from QIE, the uncomplicated and controls in frequency of HLA-DRB1*11 and 2/2 genotype of IFNγ intron 1 microsatellite. Carriage HLA DRB1*11 allele associated with ↓ IFNγ and IL-2 responses from PBMC. QIE showed differences in IL-10 promoter microsatellites R and G, and ↑ frequency TNFa receptor II 196R polymorphism. QF patients with uncomplicated recovery, differed from those with QFS/QIE, but similar in allelic frequencies to control panels	Conclusions *C.b.*, parvovirus B19 infection and CFS studies suggest that 'idiopathic' CFS patients from the wider population, away from outbreaks/occupationally exposed groups, are unlikely to have laboratory evidence of infection with the same infective agent. A common immuno-genetically determined failure of cytokine homeostasis to infective agents with the capacity to persist long in hosts is more likely	Diag	★ ★★ ★	☆☆	★★
No group differences cytokine levels. Severity symptoms ↓ in time. ↑ Age associated with ↑ musculoskeletal pain and neurocognitive disturbance. PIFS stereotyped post different triggers, with equal acute-phase cytokine production. Psychological/microbial factors not predictive PIFS. PIFS: ↑ mean no. bed-days acute phase, and more days "out of role"	Ongoing production IL-1b, IL-2, IL-4, IL-6, IL-10, IL-12, TNFa and INFγ have no role in PIFS. Evidence against hypothesis associating prolonged fatigue with altered cytokine levels. AI triggers, not drives symptoms. PIFS can persist wks to mo	B/D	★★★★	★★	★★

S4 Table. Domain aetiology (continued)

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
2009, B. Marmion [37]	Australia and UK, yr study NR	Laboratory case study	10 Birmingham (1989) *C.b.* PCR positive and 1 IE. To retest PCR positive samples with more sensitive methods for viable *C.b.* and *C.b.* cell components antigen and specific LPS ≥12 yrs post AQF, and re-interpret previous results. Review literature for a concept of immunomodulatory complex generated by current studies	3 SCID mice; spleen and liver examination by PCR (targets COM1 and IS1111a sequences), IFA	Inoculation patient sam-ples in SCID mice for 60 d
2009, L. Zhang [48]	United Kingdom, yr study and period NR. Single measurement study	CC	117 patients idiopathic CFS/ME; 6 Q-CFS/ ME. Controls: endogenous depression (n=14), blood donors (n=29). Attempt to reproduce genomic subtypes CFS/ME (with distinct: SF-36, clinical phenotypes, severity and geographical distribution), determine specificity signature CFS/ ME, and test associations CFS/ME subtype and infection by determining expression levels 88 human genes	Chalder Fatigue Scale, SF-36, Somatic and Psychological Health Report, PSQ, McGill Pain Questionnaire, PAXgene blood RNA kit, micro-spectrophoto-metry, qPCR	NA
2010, Y. Kadota [46]	Australia, 1999 (sub study DIOS); single measurement	Pros. CC	23 PIFS patients (9 RRV, 7 EBV, 4 QF, 3 viral infection unknown origin) vs. 25 matched (age, sex, BMI, activity levels) healthy controls. Evaluation association of PIFS with bidirectional autonomic signalling disturbance	Pulse oximeter, pain test algometer, Stroop task, SPHERE, SOMA K10, BDQ, DS14	NA
2010, O. Sukoche-va [36]	Australia, yr study NR, duration NR	CC (laboratory case study)	No patients/controls. Samples post AQF patients (Birmingham, 1989), 3 groups; recGr3: asymptomatic recovery post AQF. QFSGr5: QFS, no co-morbidity. QFSGr6: QFS fatigue associated co-morbidity. 12 yrs post outbreak, groups sampled *C.b.* antibody, blood leucocytes, PCR on BMA. PCR positive samples (bone marrow, PBMC, or aortic valve specimens) 10 patients from subsets inoculated intraperitoneal NOD/ SCID mice. Control animals received blood PCR negative, seronegative controls. To isolate living *C.b.* to ascertain pathological effects, retest and determine nature residual *C.b.* cell components	Cell culture assay, PCR (target COM1 and IS1111a), CBA, skin granuloma test in guinea pigs, immunoche-mistry,histoche-mistry, image acquisition	Inoculation patient sam-ples in NOD/ SCID mice, FU for infec-tion evidence and presence DNA and specific anti-gens in spleen and liver macrophages

Outcome	Conclusions/recommendations	Other domain	QA (NOS) S	C	O
All patients' specimens including heart valve with endocarditis were infection negative in SCID mice. Mice spleens and livers PCR negative. Spleen sections of all specimens showed Coxiella antigen LPS complex by IFA	Long-term persistence non-infective, biodegradable immunomodulatory complex traces genomic DNA. Immuno-modulatory complex survival >12 yrs, in 1 patient 70 yrs, implies repeated passage macrophages ↓ regulation biodegrading function. Systemic symptoms QFS may reflect wide distribution parasitized mononuclear phagocytes. QFS follows clinical overt infection, rarely subclinical infection	NA	NA		
In CFS/ME differential expression confirmed for all 88 genes. 8 genomic CFS/ME subtypes with marked differences global functioning, clinical symptoms, severity levels and geographical distribution. Q-CFS/ME similar patterns gene expression in peripheral blood to idiopathic CFS/ME, and markedly different from normal group. 5/6 Q-CFS/ME patients clustered in subtype A, but no subtype-specific relationships found with *C.b.* antibodies. Evidence subtype-specific relationships EBV and enterovirus. Gene expression in endogenous depression similar to normal controls, except ↑ regulation 5 genes (APP, CREBBP, GNAS, PDCD2, and PDCD6). Q-CFS/ME patients ↑ McGill Pain Questionnaire scores i.c.w. other groups. SF-36 ↑, Mental and physical fatigue, and SPHERE scores ↓ i.c.w. all groups, except normal blood	Q-CFS/ME had similar patterns gene expression as idiopathic CFS/ME	Diag, B/D	★ ★ ★		★ ★
PIFS patients: ↑ symptoms in general, fatigue related, or psychological distress, more days not fulfilling normal roles past mo, ↑ experience negative emotions, ↑ reporting functional impairment daily activities, ↑ resting heartbeat, ↑ sensitivity to physiological signals. Relation between heartbeat discrimination accuracy and pressure pain sensitivity. Different heart rate pattern in response to ongoing mental stressors	PIFS: ↑ interoceptive sensitivity (with strong symptoms correlation), distinct pattern cardiac response; evidence physiological hyper-vigilance and response inflexibility. ↑ Resting heart rate with ↓ heart rate variability: ↓ parasym-pathic drive. Autonomic dysfunction involves both disturbance processing incoming homeostatic information, and altered reactivity to stressors	B/D	★★★	★★	★ ★ ☆
Culture samples 10 QF patients NOD/SCID mice, 12 yrs post AQF no viable *C.b*. No AI induced. Complexes material *C.b.* antigens found in mouse spleens, significantly higher amounts in samples QFS, also in bone marrow and liver in all cases. Immunomodu-latory complex stimulate cytokine release in mice and THP-1 macrophages, and to provoke inflammatory reaction on intradermal injection into skin of QF hyperimmunized guinea pigs (with Qvax). QFSGr5 and 6: weight ↓ 1st week post inoculation, later recovered and steady weight gain consistent with absence infection. All mouse spleen specimens PCR negative (1:100 dilutions). Despite absence active infection, changes: moderate spleen enlargement QFSgr5 and 6 i.c.w. controls ($p<0.05$), no massive splenomegaly by live *C.b*. Sections mouse spleens with variable amounts aggregates stained to detect specific antigen, also in NOD/SCID mouse bone marrow and liver inoculated with QFS specimens. *C.b.* antigens no correlation low levels *C.b.*, suggests complexes to represent incompletely degraded cell material. *C.b.* antigens localized in spleen phagocytes, and *C.b.* immunomodulatory complex in lysosomes mouse splenocytes. L-6/IL-10 ratio and ↑ level IL-10 might signal important role in facilitating survival non-degraded bacterial material	In QFS viable, infective *C.b.* are rarely, if ever, isolated from PBMC or bone marrow, but complex of antigen and Phase 1 LPS (immunomodulatory com-plex) is regularly present. This non-infec-tive complex of *C.b.* antigens survives in host and provokes aberrant humoral and cell-mediated immunity responses – a possi-ble pathogenic link between initial infec-tion and PQFFS. Different responses between endocarditis, asymptomatic/ recovered and QFS patients considered due to immunogenetic differences in handling immunomodulatory complex and cytokine responses. Hypothetical pathogenetic sequence QFS; overt clinical QF and immunogenetic polymorphism--> defective antigen clearance (immune-modulatory complex persistence)--> persistent cell-mediated immunity and cytokine dysregulation--> cytokine-mediated somatic gene modulation--> QFS	NA	NA		

S4 Table. Domain aetiology (continued)

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
2011, S. Galbraith [47]	Australia, yr study NR (sub study DIOS). Study period: baseline measure (T1 0<6 wks), T2 6<12 wks, T3 3<9 mo or >9 mo, T4 >12 mo, FU after 2 and 4 wks	Longitudinal, nested CC	Caucasians with PIFS (n=18; EBV, RRV, *C.b.*) (mean age: 40, SD18 years). Matched (age, sex & infection type) controls (n=18) who recovered promptly (mean age: 39, SD16). 11 ♂ per group. 127 samples analysed, 3-4 time points/subject. In longitudinally collected samples peripheral blood transcriptomes studied for gene expression patterns in PIFS patients and controls. Differential expression sought between early illness and late recovery (within-subject comparison), PIFS cases and recovered controls (between subjects comparison), and genes correlated with end phenotypes derived by principal components analysis (between-cohorts)	Microarray and confirmatory qPCR. SPHERE, SOMA	NA
2012, B. Piraino [60]	Australia, yr study NR (sub study DIOS). Study period NR. Baseline, FU 2-3wks, 4-6wks, 3-mo interval until 12 mo post AI	CoS	Caucasians (mean age 34.2, 49% ♀), <6 wks post AI (n=296), EBV, RRV, QF. Princi-pal components analysis acute phase, self-report symptom data to empirically derived indices fatigue, pain, neuro-cognitive difficulties, mood disturbance, overall illness severity. Apply endophenotype concept to clinical dataset describing symptom domains of acute sickness response post viral/non-viral pathogens, and validation by showing association with SNP in cytokine genes (IL-6, TNFa, IFNy, IL-10)	SPHERE (and SOMA), PSC, BDQ, principal component analysis, NanoDropR ND-1000 (DNA quantification), Sequenom MassARRAY® (genotyping of SNP)	NA
2012, H. Hussain-Yusuf [49]	UK, 2008	CC	Cohort 211 UK factory workers *C.b.*-exposed 2002. FU 6 yrs post outbreak, comparison QF serology, presence viable *C.b.*, its DNA and fatigue in post AQF cases (n=38, 3 uncertain serology 2002) vs. seronegative, same outbreak (n=14). Assess if *C.b.* antigens (immunomodulatory complex) remain undegraded in some post AQF, with abnormal cytokine profile causing ongoing fatigue	Chalder Fatigue Scale, qPCR (com1 gene) on PBMC and VERO cultures (detect *C.b.* DNA), IFA, SCID mice inocula-tion (detect viable *C.b.*)	NA

Outcome	Conclusions/recommendations	Other domain	QA (NOS) S	C	O
23 genes with modest differential expression (0.6-2.3-fold change) in within-subject comparisons of early, symptomatic time points with late, recovered time points. Modest differences 63 genes, in CS comparison cases-controls 6 mo post AI in regression model. 223 genes correlated with individual symptom domains. qPCR confirmed 33/45 genes, none consistent across cohorts. Within subject comparison: 12 subjects (5 with QF) T1 SOMA scores ≥3, T4 SOMA scores <3. No genes with adjusted significance <0.05. Relative lack variance gene expression levels over ≥12 mo. Between subject comparisons: 17 cases (6 QF), 11 controls (2 QF). No genes with adjusted significance <0.05. QF subjects predominantly ♂ and older. 13 genes adjusted significance <0.05, 1 (CYBA) associated with fatigue in 2 of 3 infective cohorts (EBV, QF). Analysis identified illness severity, fatigue and neurocognitive disturbance, correlated for EBV and QF cohorts. Correlation test: 96 genes unadjusted significant at 5% for EBV and QF for severity, 93 for fatigue symptom domain, 106 for neurocognitive disturbance. Repeated correlation analysis: no genes correlated for EBV and QF in association with severity, fatigue, neurocognitive disturbance	Several infections trigger PIFS, which share key illness characteristics with each other and CFS. Previous CS CC studies of CFS suggested unique gene expression signature in peripheral blood samples. Although illness characteristics of PIFS patients have more similarities than differences, no reliable peripheral blood gene expression correlate is evident. No genes consistently associated with illness. CFS incidence closely comparable between EBV, RRV, *C.b.* Lack of coherent set of gene expression correlates across cohorts argues against validity of previously proposed signatures for PIFS or CFS. PIFS likely to be truly post-infective, un-associated with ongoing active replication of triggering agent	NA	★ ★ ★ ★	★ ★	★ ★
Individual symptom indices correlated with overall severity and functional status. Domain scores stable over time within subjects, but varied between subjects with same infection, and across infection sub-cohorts. Overall illness severity may have been comparable in some subjects, relative contributions from individual symptom domains making up the illness complex varied between these subjects. T allele IFNγ+874T/A SNP best predictor of ↑ fatigue. ♀ more likely grouped in ↑ fatigue extreme. C allele of IL-10-592C/A SNP exerted protective effect on neurocognitive difficulties. A allele IL-10-592 SNP and G allele IL-6-174G/C SNP associated ↑ mood disturbance	Acute illness response has discrete symptoms including fatigue with unique genetic associations. Study offers new pathophysiological inside fatigue states. Illness severity phenotype not dependent on age/sex/infection subtype. Robust correlation between illness severity and reported disability in AI. ♀ over represented in high severity group fatigue, mood disturbance, neurocognitive difficulties	NA	★ ★ ★	★ ★	
18% became seronegative, remainder 10 phase I, 21 phase I en II antibodies. 29% controls became seropositive. No patient/control PBMC contained viable *C.b.*/DNA. No viable *C.b.* in PMBC tested in cell culture and SCID mice inoculation. Chalder Fatigue Scale score after 6 yrs (n=11): 4 significant fatigue, 4 some, 3 not fatigued. No relationship between fatigue levels and serology, nor with presence of viable *C.b.*/DNA	6 yrs post AQF, some patients became seronegative but none contained viable *C.b.*/DNA in their PBMC. Correlation PQFF and persistent DNA could not be examined. A more sensitive DNA assays or more invasive sampling needed to test hypothesis. IgGII most useful to test past QF exposure	B/D	★ ★ ★ ★		★ ★

S4 Table. Domain aetiology (continued)

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool	intervention
2014, M. Kremers [63]	Netherlands, yr study 2013-2014. Study period: April- August 2009, FU 4 yrs post AQF	CoS	102 seronegative PCR positive, symptomatic, AQF patients (64.7% ♂, mean age 48, SD16, range 17-85); 24 hospitalised. 93 FU 3, 6 or 12 mo for IFA IgGI and II. NCSI 4 yrs post AQF (n=58). Assess if ↑ CRP AQF coincides with ↑ IL-6 and if levels correlate with *C.b.* DNA load and disease severity, expressed by hospital admission and fatigue development	NCSI, PCR (Ct value), IFA, CRP, IL-6	NA

**** Definition of used study population in articles explained in a different table, including definitions of QFS and/or fatigue is applicable. Main information is on aetiology. Some articles also contain relevant information on other domains: Diag= Diagnosis, B/D= Background/descriptive, P/T= Prevention/therapy***

Abbreviations: 2-5AS= 2',5'-oligoadenylate synthetase, AI= Acute infection, AQF= Acute Q-fever, BDQ= Brief Disability Questionnaire, assessment of the impact of illness on functional capacity, and days out of role quantified the days over the past months the respondent was unable to carry out usual daily activities fully, BMA= Bone marrow aspirate, BMI= Body Mass Index, *C.b.= Coxiella burnetii,* CBA= Cytometric bead array, uses the sensitivity of amplified fluorescence detection by flow cytometry to measure soluble analytes (e.g. interleukins) in a particle-based immunoassay, CC= Case-control study, CDC= Centres for Disease Control and Prevention, CF= Chronic fatigue, CFS(/ME)= Chronic fatigue syndrome (/myeloencephalitis), CFT= Complement fixation test, CIDI= Composite international diagnostic interview to screen for any history of depression, anxiety or somatisation disorder. This computerised program formulates ICD-10 and DSM-III-R diagnoses and records current as well as pre-existing psychiatric morbidity, CoS= Cohort study, CRP= C-reactive protein, CS= Cross-sectional, DIOS= Dubbo Infection Outcomes Study**,** cohort study of subjects ≥16 yrs followed from the onset of a confirmed and documented AI due to EBV; *C.b.*; or RRV ≤6 wks post AI until complete recovery, DS14= Distressed personality scale, assessment of negative affectivity (an enduring tendency to experience negative emotions) and trait social inhibition (the tendency to feel inhibited, tense, and insecure when with others), DTH= Delayed-type hypersensitivity, to assess cell-mediated immune function in vivo, EBV= *Epstein-Barr virus*, ECG= Electrocardiography, FU= Follow-up, GHQ= General health questionnaire, 12-item questionnaire to detect current cases of psychiatric co-morbidity, I.c.w.= In comparison with, IFA= Immunofluorescence assay, IFN= Interferon, IgG= Anti-phase IgG, IgGI= Anti-phase IgG I titre, IgGII= Anti-phase IgG II titre, IL= Interleukin, IS= Insertion sequence, K10= Kessler 10, to assess current psychological distress, LMR= Lymphocyte mitogenic responses, LPS= Lipopolysaccharide, Mo= Month(s), MUGA scan= Multi Gated Acquisition Scan (gated cardiac radio-nuclide scans), a time-proven nuclear medicine test to evaluate the function of the right and left ventricles of the heart, allowing informed diagnostic intervention in heart failure, NA= Not applicable, NCSI= Nijmegen clinical screening instrument, originally developed to provide a detailed assessment of health status of COPD patients. It combines a number of existing health status questionnaires, NOS= Newcastle–Ottawa Scale: S= selection (maximum of 4 stars), C= comparability (maximum of 2 stars), O= outcome (maximum of 3 stars); ★: star earned; ☆: item not applicable, N/No= Number (of), (n-)PCR= (nested-) Polymerase chain reaction, NR= Not reported, Pain test algometer= For pressure pain threshold test to measure pain sensitivity, PBMC= Peripheral blood mononuclear cells, PHA= phytohaemagglutinin, PIF(S)= Post-infective fatigue (syndrome), PO= Personal opinion, POMS= Profile of Mood States to assess current mood status. This instrument includes 7 subscales: 'fatigue', 'depression', 'anxiety', 'vigour', 'anger', 'friendliness', and 'confusion', PQFF= Post-Q-fever fatigue, PQF(F)S= Post-(acute)Q-fever (fatigue) syndrome, Pros.= Prospective, PSC= Physical Symptoms Checklist, consisting of 51 symptom items, PSQ= Pittsburgh Sleep Questionnaire, to assess sleep abnormalities, QA = Quality assessment, Q-CFS(/ME)= Q-fever induced chronic fatigue syndrome (/myeloencephalitis), QF= Q-fever, QF(F)S= Q-fever fatigue syndrome, (Q)IE= (Q-fever induced) Infective endocarditis, Ref= Reference, RRV= *Ross River virus*, SCID= Severe combined immunodeficiency, SD= Standard deviation, SF-36= The Short Form (36) Health Survey, a patient-reported survey of patient health to assess quality of life of patients, functional impairment and reduced health related quality of life, SNP= Single nucleotide polymorphism, SOFA= Schedule of Fatigue and Anergy to identify cases of chronic fatigue syndrome. The subject rates 10 items on a 4-point scale. Subjects

Outcome	Conclusions/recommendations	Other domain	QA (NOS) S	C	O
92 patients ↑ IL-6, 101 ↑ CRP during AQF. Significant weak negative correlation *C.b.* DNA loads, IL-6 and CRP, significant moderate-strong positive correlation IL-6 and CRP. Hospitalised patients: ↑ IL-6 and CRP than the non-hospitalised, *C.b.* DNA load equal. NCSI: 58 respondents, 34 abnormal outcome (58.6%) mild and severe fatigue. No difference in Ct values, CRP and IL-6 in AQF between patients with normal outcome and abnormal outcome subdomain fatigue	Correlation IL-6 and CRP in AQF points to immune activation pathway in which IL-6 induces CRP. Differences IL-6 and CRP between hospitalised vs. the non-hospitalised despite identical DNA load suggest an important role for host factors. ↑ IL-6 and CRP seems predictive of more severe disease. No support that IL-6 or CRP levels during AQF are prognostic for fatigue development	NA	★ ☆★		★ ★

who score ≥3 items as 'a good part of the time' or 'most of the time' are classified as cases of 'fatigue/neurasthenia', SOMA= Empirically derived subscale of the SPHERE, used to record PIFS or illness duration. This reliably predicts disability and reflects patients' and doctors' reports of reasons for presentation to primary care. Scores ≥3 represents a clinically-significant fatigue state. Provisional PIFS: SOMA scores ≥3 at all time points up ≤3 months. Confirmed PIFS: symptoms persisted >6 months, and alternative explanations for ongoing illness was excluded. SPHERE= Somatic and Psychological Health Report, to assess a wide range of physical and psychological symptoms, including severity and duration of symptoms, Stroop task= To assess cardiac response, TGFB= Transforming growth factor beta, TNF= Tumor necrosis factor, UK= United Kingdom, Wks= Weeks, Yr(s)= Year(s)

S5 Table. Domain prevention/therapy

Ref	Country, yr study, period and duration	Study type	Patients, controls, characteristics, co-morbidity*	Tool
2004, Y. Arashima [6]	Japan, yr study NR. Period: Jul-Nov 2001, baseline, 4, 8 and 12 wks post start treatment	CoS	20 QFS patients (3 ♂, mean age 34.6±5.7) with subjective symptoms (duration 20.8±3.3 mo, range 3 mo-4 yrs): fatigue (20/20), slightly elevated body temperature (17/20), arthralgia or myalgia (10/20), headache (12/20), cough or sore throat (16/20), ↑ sweating (10/20), and gastrointestinal symptoms (13/20). To address presence post QFS in Japan, and evaluation of minocycline for post QFS in changes in subjective symptoms, *C.b.* antibody titres and *C.b.* DNA. No controls	Questionnaires (assess severity of subjective symptoms), PS score, IFA, n-PCR. Antibiotic side effects evaluated by interview and laboratory examination results
2005, E. Iwakami [39]	Japan, May 2001-March 2003. Period: baseline, 3 mo treatment	CoS	4/8 CFS patients (2 ♂; 1 with IgGII 1:128; 3 with *C.b.* DNA positive); mean age 29, SD4, range 23-33, duration complaints: 52.0 mo, SD55.3, range 8 mo-11 yrs. Fatigue (PS score 7±1.2), slightly elevated body temperature, headache, arthralgia/myalgia (100%), cough/sore throat (75%). 54 QFS patients (10 ♂) positive *C.b.* DNA (n=34), IgMII ≥1:32 (n=15)/IgGII ≥1:128 (n=34); mean age 38, SD16, range 11-77, duration complaints: 21.1 mo, SD24.3, range 1 mo-10 yrs. Fatigue (PS score 5.3±2.4), slightly elevated body temperature (100%), headache (63%). To explore *C.b.* in CFS by antibiotic treatment, monitor symptom changes, PCR and *C.b.* antibodies	n-PCR, *C.b.* antibodies initial examination and 3 mo after start treatment. Questionnaire survey, PS
2007, D. Ledina [5]	Croatia, yr study NR, study period: 2000-2004	Case-series	N=3 post AQF with PQFS. 2 ♂ (34 and 30 yrs), 1 ♀ (30 yrs). Initial treatment AQF: erythromycin and gentamycine 2 wks (n=1), doxycycline 2 wks (n=2). Emphasize existence and incidence CFS post AQF according to CDC CFS criteria, and show effects antibiotic treatment in QFS	Questionnaires before and after treatment for subjective symptoms. Noted in 4 degrees absent-severe
2013, S. Keijmel [42]	Netherlands, yr study: 2011-2015	RCT protocol	Objective: include 180 QFS patients, ♂ and ♀. Evaluation of efficacy of long-term doxycycline and CBT in QFS-patients	CIS; SIP total score, total score SCL-90, *C.b.* PCR and serology
2013, S. Yakubo [41]	Japan, yr study NR	CR	♀ 71 yrs, 6 yrs post AI with general malaise, spasm left hand, slightly elevated body temperature. Co-morbidity: NR. Negative n-PCR for *C.b.*, IgMI and IgMII <1:16, IgGI <1:16, IgGII 1:32	n-PCR, IFA
2013, S. Yakubo [40]	Japan, yr study NR	CR	♂ 13 yrs, fatigue and severe malaise, slightly elevated body temperature, arthralgia, myalgia, lassitude, disease period 2 mo earlier. Extended period no school attendance. Co-morbidity: NR. IFA IgMII and IgGII negative, n-PCR positive	n-PCR, IFA

Intervention	Outcome	Conclusions/ recommendations	Other domain	QA (CR or NOS) S	C	O
3 mo: minocycline 100mg/d (n=18)/ erythromycin 400mg/d (n=1)/ levofloxacin 200mg/d (n=1)	No leucocytosis or ↑ ESR. Slightly ↑ CRP 5 patients. All 7 who had been DNA positive, became negative with improvement subjective symptoms. IgM and IgG antibodies became negative post treatment. Clinical picture all patients improved: general fatigue (20/20), ↓ body temperature (12/17), gastrointestinal symptoms (10/13) and headache (9/12). PS score related to fatigue unchanged in 2 mo, but finally ↓, PS scores ↑	Minocycline administration useful for improving chronic nonspecific symptoms considered to be post QFS, and should be first-line drug for QFS. Observations may reflect existence of live *C.b.* in QFS patients	Diag, B/D	☆★ ☆	☆ ☆	★ ★★
3 mo: minocycline 100mg/d (n=29)/ doxycycline 100mg/d (n=26)/levofloxacin 200mg/d (n=3)	All 58 patients tested *C.b.* after treatment; all n-PCR positives became negative. CFS group (n=4): no improvement PS (p=0.422), no difference pre- and post-treatment temperatures (p=0.07) or headache (p=0.39) scores. QFS group: PS scores improved (p<0.001), temperature (p<0.001) and headache scores ↓ (p<0.001) post treatment	Possibility direct involvement *C.b.* pathological state CFS low. Different response to tetracycline suggest direct *C.b.* involvement pathological state QFS. Latent *C.b.* infection not involved either onset CFS or appearance symptoms	Diag, B/D	★ ★		★ ★
Case 1: 9 mo doxycycline 200mg/d + ciprofloxacin 1000mg/d. Case 2: ciprofloxacin 1000mg/d 2 mo, then doxycycline 200mg/d 4 mo. Case 3: 1 mo corticosteroids, then 3 mo doxycycline	Case 1: still fatigue after physical activity (disappears after 30 min rest) and low intensity headache. Muscle pain and slightly elevated body temperature disappeared. No criteria CFS post-treatment. Case 2: regression symptoms, except minor headache. No criteria CFS post-treatment. Case 3: still fatigued, disrupted sleep, headache, muscle and joint pains, still fulfils CFS criteria post treatment	Results prolonged antibiotic treatment CFS inconsistent. Diagnostic criteria and therapeutic recommendations for PQFS require further investigation	Diag, B/D	9/18 criteria **		
24 wks of: placebo, doxycycline 200 mg/d, or CBT	Still treating patients	NA	Diag	NA		
Kampo formula Tsumura Shakuyaku-Kanzo-To granules (7,5g/d) 3 mo	Alleviation of stiffness in hand and arm after 2 days treatment, symptom disappeared completely. 6 mo after start treatment reappearance stiffness and IgGI 1:128	QFS may feature intermittent muscle spasms, ameliorated by Shakuyaku-Kanzo-To granules, warrants further research	NA	-/-,-, +, +, +, NA,-/-,-/-		
Kampo formula Tsumura Hochu-ekki-To granules (7,5mg/d) 1 mo, then erythromycin 800mg/d 1 mo, then doxycycline 200mg/d 1 mo, then erythromycin 800mg/d at least 6 mo	Slight improvement 1 mo post erythromycin, none post doxycycline, fever stopped after long-term erythromycin, general malaise continued. Improvement after continued treatment	Consider *C.b.* as possible cause in cases of long-term school absence due to severe malaise similar to that caused by CFS	Diag, B/D	-/-, +, -/-, +/-, +/-, NA, +/-,-/-		

**** Definition of used study population in articles explained in a different table, including definitions of QFS and/or fatigue is applicable. Main information is on prevention/therapy. Some articles also contain relevant information on other domains: Diag= Diagnosis, B/D= Background/descriptive, A= Aetiology***

***** Quality assessment for case-series was performed with a quality appraisal tool making use of 18 criteria with a considered acceptable quality if at least 14 criteria were scored (≥70%) [24]***

Abbreviations: AI= Acute infection, AQF= Acute Q-fever, *C.b.= Coxiella burnetii,* CBT= Cognitive behavioural therapy, CDC= Centre of Disease Control, CFS= Chronic fatigue syndrome, CIS= subscale fatigue of the Checklist Individual Strength, to indicate the level of fatigue experienced in the previous two weeks, measured with eight items on a seven-point Likert-scale (range 8–56), CoS= Cohort study, CRP= C-reactive protein, CR= Case-report, ESR= Erythrocyte sedimentation rate, IFA= Immunofluorescence assay, IgG= Anti-phase IgG, IgGII= Anti-phase IgG II titre, IgM= Anti-phase IgM, IgMII= Anti-phase IgM II titre, Mo= Month(s), NA= Not applicable, NOS= Newcastle–Ottawa Scale: S= selection (maximum of 4 stars), C= comparability (maximum of 2 stars), O= outcome (maximum of 3 stars); ★: star earned; ☆: item not applicable, N/No= Number (of), (n-)PCR= (nested-) Polymerase chain reaction, NR= Not reported, PQFS= Post-(acute)Q-fever (fatigue) syndrome, PS= Performance status score (range 0-9), which reflects the grade of fatigue/malaise to assess the severity of CFS, QA-CR= Quality assessment; for CR no quality checklists are available. Therefore, the following eight criteria for quality assessment were determined; addressing an appropriate and clearly focused question, representative population, description of the survey method or data collection, outcome measures defined, outcome measures described, response rate reported and results valid and applicable to the patient group targeted. The articles scores on these items:-/-,-, +/-, +, or ++, based on the Coordination of Cancer Clinical Practice Guidelines in Europe criteria, RCT= Randomised controlled trial, QF(F)S= Q-fever fatigue syndrome, Ref= Reference, SCL-90= Symptom Checklist 90, to measure the level of psychological distress, consisting of 90 items scored on a five-point Likert-scale (range 90-450), SD= Standard deviation, SIP= Sickness Impact Profile, to measure the level of functional impairment. A total score is derived out of the scores on the subscales: sleep-rest, household, mobility, social interactions, walking, alertness and intellectual functioning, work, and recreation, Wks= Weeks, Yr(s)= Year(s)

9

S6 Table. Grey literature

Ref	Country, yr study, period and duration	Docu-ment	Patients, controls, characteristics, co-morbidity	Tool
1992, M. Shannon [1]	Australia, yr study NR, study period NR	Thesis	Abattoir workers (n=117), immune status assessed 1981-1986. Group of clinical history AQF and serology CFT Phase I and II, and IFA (n=39). All either ↑ CFT antibody titre and/raised IFA IgM as indication current QF. Unexposed comparison cohort (n=39): vaccinated and non-vaccinated (seropositives without clinical history AQF). Occurrence infection not noted	*C.b.* CFT, IFA, questionnaires
2009, B. Marmion [2]	Australia and UK, yr study NR, study period NR	Book (chap-ter)	No patients/controls. Characteristics and co-morbidity: NR. Experience from several studies	NA
2011, C. Tempel-man [3]	Netherlands, yr study 2011	Report on eco-nomic evalua-tion	Economic costs –human and veterinary Dutch QF outbreak 2007-2010 assessed with 4024 notification AQF. Assumptions: 25% (n=503) AQF get QFS duration 5-10 yrs. Results: quality of life ↓, assumed period sick leave 5-10 yrs, productivity 50% ↓. Assumption 60% of those with QFS were gainfully employed	Interviews, public data outbreak
2012 Guideline working group on QFS [4]	Netherlands, yr study 2011-2012	Guideline	Achieve uniformity diagnosis and treatment QFS	QFS and CFS literature and multidiscipline-ry consensus

These documents contain relevant information for the domains: Diag= Diagnosis, B/D= Background/ descriptive, A= Aetiology, P/T= Prevention/therapy. Main domain indicated in bolt

Abbreviations: ALT= Alanin aminotransferase, AQF= Acute Q-fever, BMI= body mass index, *C.b.= Coxi-ella burnetii,* CBT= Cognitive behavioural therapy, CFS= Chronic fatigue syndrome, CFT= complement fixation test, CK= creatine kinase, CRP= C-reactive protein, CQF= chronic Q-fever, ESR= Erythrocyte sedimentation rate, IFA= Immunofluorescence assay, IL= Interleukin, Mo= Month(s), NA= Not applica-ble, NR= Not reported, QF= Q-fever, QF(F)S= Q-fever fatigue syndrome, Ref= Reference, TSH= thyroid stimulating hormone, Yr(s)= Year(s)

Outcome/advice	Conclusions/recommendations	Domains	QA
Definition QFS; laboratory proven, clinically manifest QF, commences within 12 mo of illness, duration ≥6 mo. 5 major symptoms; 1. fatigue of 2-≥7dys, ≥6x/yr continuously with some absence from work, 2. malaise – as above except work, 3. muscle twitches/ fasciculations, 4. nausea ≥6x/yr, 5. abnormal sweating ≥10x/yr, might be accompanied by other symptoms. Most subjects healthy before AQF regarding depression. Mental problems; depression, lack of concentration, impairment short memory, mood lability, altered sleep pattern following AQF. Some general practitioners stated that tricyclic antidepressants were beneficial. 30-40 cases/1000 abattoir workers/yr, each costs 2-88.000 in medical care and loss of wages, endocarditis 50-10.000/yr, QFS 20-50.000/yr. Duration QFS 6 mo-20 yrs	Approximately 23% develops QFS post overt AQF. No grounds to dismiss QFS as a psychiatric depressive illness. Aetiology is unclear, might be due to immune stimulation and a disordered function of the lymphocyte-macrophage interaction. Same pathways to mood change may be involved in depression and QFS and altered by chemotherapy	**B/D**, P/T	NA
Start often 6 mo-1 yr post AQF. Symptoms complex not limited to fatigue, also nausea, headache, night sweats, myalgia, arthralgia, fasciculations, painful lymph nodes, disturbed sleep pattern, anger, ↓ concentration, mental acuity ↓. Duration: >1 yr, often 5-10 yrs. Antigens in samples SCID mice, cellular immune response heightened, cytokine dysregulation: IL-6 ↑, IL-10, IL-2 ↓, low fever. Pathogenesis; no consensus. Bacteraemia restricted by humoral and cell-mediated immunity, by product clearing *C.b.* DNA containing components with an immunomodulatory effect. Cell-mediated immunity and dendritic cells causing dysregulation, cytokines and other immune mediators give rise to symptoms	In Australia QFS is the most common chronic sequel of AQF affecting 10-15% of patients. It usually follows AQF and rarely if ever subclinical infection	**B/D**, A	NA
QFS duration 5-10 yrs costs ↓ quality of life 55.6-104.7 million euros. Costs of sick-leave due to QFS are not separately presented but together with CQF and therefore not mentioned	Economic costs due to QF outbreak are considerable as the course of disease especially due to QFS is protracted and reflected in ↓ quality of life, ↓ productivity, and ↓ income	**B/D**	NA
QFS definition: severe fatigue causing significant disabilities daily life ≥6 mo, reference to lab confirmed AQF, not caused by somatic/psychiatric co-morbidity, fatigue absent before AQF/significantly ↑ since. Diagnosis on history, physical and laboratory examination excluding other causes of fatigue (including ESR, CRP, CK, TSH, leukocytes with differentiation, creatinine, alkaline phosphatase, ALT, glucose, ferritin, urinary sediment). Cave diagnosis in case of morbid obesity (BMI>40) or substance abuse. Impossible to diagnose QFS in case of: depression/depression preceded current symptoms, schizophrenia, psychoses, any type dementia, eating disorders, unless resolved ≥5 yrs	Advice patients ≤6 mo post AQF: i) stay mentally/physically active, adjust pace if necessary; ii) alternate activities, also within activities; iii) keep fulfilling daily role; iv) keep steady sleep-wake pattern; v) avoid focussing on fatigue; vi) focus on feasible activities, appreciate accomplishments. Advice CBT/GET after QFS diagnosis. GET might be an additional treatment strategy	**Diag**, B/D, A, P/T	NA

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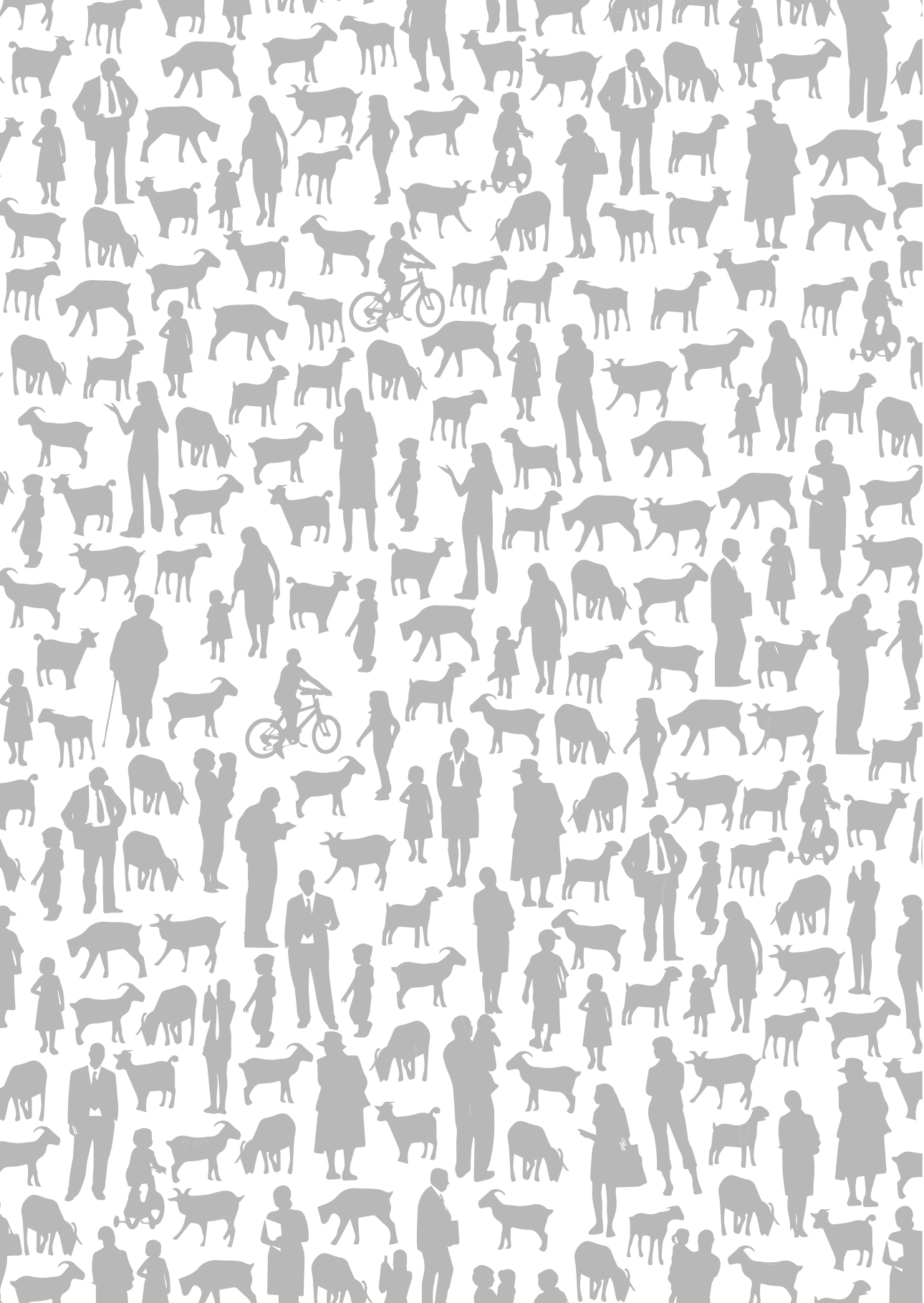

Chapter 10

SUMMARISING DISCUSSION

SUMMARISING DISCUSSION

Chapter 2 is descriptive; sketches the Q-fever outbreak from 2007 to 2010 and provides general information on *C. burnetii* diagnosis, sequels of infection and veterinary control measures.

Part I. Serological screening for chronic Q-fever

Chapter 3, Large regional differences in serological follow-up of Q-fever patients in the Netherlands

Previous knowledge on this subject

Acute Q-fever may progress to chronic Q-fever in about 2% [1] of patients. Serological follow-up of acute Q-fever patients is essential in order to identify and ensure timely treatment of chronic Q-fever [2-4]. However, national or international guidelines on serological follow-up were not available at the time of the Dutch epidemic.

The Municipal Health Service (MHS) Hart voor Brabant received information from patients and health professionals, suggesting that not all Q-fever patients received serological follow-up and that there might be regional differences in follow-up procedures.

The aim of the study and what was examined

The aim of this study was to investigate the extent to which acute Q-fever patients received serological follow-up, identify regional differences in the organisation, knowledge and practices among medical practitioners regarding serological follow-up.

We used data of 3,198 patients diagnosed with acute infection by three Laboratories of Medical Microbiology (LMM) in the province of Noord-Brabant between 2007 and 2009. One LMM offered active follow-up by sending patients a reminder while the other two LMMs only tested at the physicians' request. The follow-up rate of the two systems was compared. In addition, the knowledge regarding Q-fever of 209/501 general practitioners (GPs) and 32/112 medical specialists was investigated with a questionnaire.

What this study adds

- The serological follow-up of acute Q-fever patients, among the three laboratories ranged from 25% to 95% [5].
- Up to 95% of patients responded to active recall for serological follow-up
- If recall depended on GPs/specialists, 25% of patients received serological follow-up.
- Two thirds of GPs and specialists correctly identified risk groups for chronic Q-fever.
- 35% of GPs and 22% of medical specialists never requested serological follow-up.
- 63% of GPs and 45% of specialists assumed that an MHS or LMM organized serological follow-up.

Recommendations as a consequence of this study

- Active recall of patients by a LMM ensures the best follow-up rate for Q-fever. Active recall could also be considered for other infectious diseases that require serological follow-up. It is advisable to discuss with laboratories, medical practitioners and patient organisations or groups what recall system could work best in a given situation.
- Provide every patient diagnosed with acute Q-fever an explanatory leaflet on the importance of serological follow-up and laboratory forms with dates for follow-up. This could be done by the health care provider/assistant.
- Incorporate recommendations for serological follow-up in national guidelines.

Chapter 4, Strategies for early detection of chronic Q-fever; a systematic review

Previous knowledge on this subject

International literature suggested at least two serologic tests (at three and six months) during the first year after an episode of acute Q-fever [3, 4, 6]. In 2008 Dutch authors [7] advised tests at three, six, and twelve months after diagnosis. Three years later, distinguishing between low and high risk patients was suggested for serological follow-up tests: for the first group once at nine months, and for the second group at three, six, nine, and twelve months [8]. Recommendations from individual studies on follow-up and screening strategies for early detection of chronic Q-fever exist but international guidelines were not available.

The aim of this study and what was examined

The aim of this study was to assess the evidence base for different follow-up and screening strategies for early detection of chronic Q-fever. Criteria for those at risk of a chronic infection, frequency, optimum timing, intervals, and duration of follow-up were also considered.

By conducting a systematic literature review, all relevant literature available from PubMed or Embase up to 17 October 2012 was assessed which resulted in the inclusion of 20 articles.

What this study adds and its recommendations

- There was no consensus in definitions or follow-up strategy. Most studies suggested serological follow-up of acute Q-fever but information on timing, frequency and duration was inconsistent.
- Only acute Q-fever patients with a clinical indication of a cardiac valve abnormality should be subjected to echocardiography.
- Provide frequent, e.g. every three months, serological and clinical follow-up for acute Q-fever patients with known risk factors. Provide follow-up once during the first year – but after three months for example at 6 or nine months- for those without a known risk factor.

- Establish national and international guidelines on the serological and clinical follow-up of acute Q-fever patients.
- Consider in outbreak situations serological screening of risk groups for chronic Q-fever for *C. burnetii.*

Chapter 5, Population Screening for chronic Q-fever seven years after a major outbreak

Previous knowledge on this subject

In 2007, 25% of sampled inhabitants of Herpen, the first Dutch village affected by the Q-fever outbreak, were seropositive [9]. Between 2007 and 2010 this village was in the proximity of four *C. burnetii* positive goat farms. Two of these farms had *C. burnetii* induced abortions in April 2007 and May 2008. The closest farm was in the village and the furthest six kilometres away from the village centre.

An immune fluorescence assay (IFA) IgG antibody titre phase I ≥1:1,024 during follow-up is an important marker of chronic infection [8].

The aim of the study and what was examined

Seven years after the outbreak started, we measured the serological *C. burnetii* status of inhabitants of the village Herpen in order to identify chronic Q-fever infections including those that occurred after an asymptomatic *C. burnetii* infection. This in order to offer timely treatment to those with chronic Q-fever and assess whether large-scale population screening elsewhere in the outbreak area is warranted.

The serological *C. burnetii* status of 1,517 adult inhabitants (>70% response) was measured with the Immuno Fluorescence Assay (IFA). An IFA cut-off of IgG phase I or II of ≥1:64 indicated a past *C. burnetii* infection. Participants with an IgG phase I ≥1:512 [10] were considered at risk for chronic Q-fever and referred for clinical examination to confirm or reject this diagnosis.

What this study adds

- Seven years after the outbreak began, 513/1,517 (34%) participants had antibodies against *C. burnetii*.
- Of the participants that were IFA positive in 2007, 17% seroreverted and had become seronegative by 2014. Taking this into account approximately 41% of participants were estimated to have been infected with *C. burnetii*.
- Six participants, 1.2% of seropositives, had an IgG I ≥1:512. All were PCR negative. Two had been diagnosed previously with chronic Q-fever. The other four were clinically examined. One of these four participants, a male >65 years, with an increased erythrocyte sedimentation rate, renal insufficiency, diabetes mellitus type 2, and a cardiac murmur , was diagnosed with chronic Q-fever. He had no episode of acute Q-fever in his medical history.

- Of the 69 participants with known cardiovascular risk factors, 16 (23%) were IFA-positive. Three had received the Q-fever vaccine, while 13 were naturally infected. Two of these 13 participants (15%) developed chronic Q-fever.
- Screening the general adult population of Herpen seven years after the beginning of an outbreak identified one individual (1/1,517) with previously undetected chronic Q-fever.

Recommendations as a consequence of this study

- Screen patients with known cardiovascular risk factors for chronic Q-fever, for *C. burnetii* infection as soon as an outbreak is detected and vaccinate the innate.
- Beware of seroreversion. Realise that negative *C. burnetii* serology (IFA) does not rule out a previous infection. Take this into account when vaccinating high risk groups against Q-fever.
- GPs in a high incidence area ought to be aware that chronic Q-fever can develop after an a-symptomatic *C. burnetii* infection.
- General population screening for chronic Q-fever, seven years after the beginning of an outbreak, appears to have a low yield.

Discussion part I

It is essential that individuals diagnosed with acute Q-fever are informed about the risk of developing chronic Q-fever and the importance of serological follow up and that they also receive this follow up [5] especially during the first year after infection [10]. Informed patients could request this follow-up when not offered by their health care provider. During the Dutch outbreak serological testing within one year after acute Q-fever, detected 98% [10] of chronic Q-fever patients.

The delay between development and diagnosis of chronic Q-fever after asymptomatic infection is unknown. Chronic Q-fever can be detected years [4, 11] after the initial infection in the absence of screening. Undetected chronic Q-fever cases are likely to have been the initially symptomatic infected that did not seek medical care or did not receive proper follow-up after the acute episode or those with an initial asymptomatic infection. Of all chronic Q-fever cases, registered in the Dutch database – the minority- 38% recalled an acute Q-fever episode [12]. Follow-up of asymptomatic or undiagnosed *C. burnetii* infections and or screening those with an undiagnosed risk factor in order to identify chronic Q-fever is impossible. Population screening [13], years after a large outbreak, required a considerable effort and investment and had a small yield [13].

Immediate openness about a Q-fever outbreak and informing medical practitioners' and the general public about serological follow-up and possible long-term complications, together with an active serological follow-up system is essential for timely identification of chronic Q-fever. That way both the public and the GP will not only be aware of acute Q-fever

infections during an outbreak but might be more vigilant in the future regarding chronic Q-fever. There was a limited vaccination campaign after the outbreak in 2011. The percentage of the at risk for chronic Q-fever that were vaccinated is low [4] (see also Chapter 5). It is unclear if this is due to the selection procedure of the treating medical doctor or if patients decided against vaccination. Again, informing both medical doctors and the population in an outbreak area might enable those at risk to make their own informed choice.

Part II. The health status especially fatigue and work after a *C. burnetii* infection

Chapter 6, Self-reported sick leave and long-term health symptoms of Q-fever patients

Previous knowledge on this subject

National or international studies, on sick leave or the ability to work at individual or Q-fever patient group level, were unavailable in 2009 through searching Pubmed.

The MHS Hart voor Brabant repeatedly received questions from occupational health physicians, GPs, medical specialists and patients regarding the post Q-fever impact on persisting symptoms in particular fatigue and consequences for work.

The aim of the study and what was examined

The objective was to assess the frequency and duration of sick leave, symptoms and associated risk factors, 12 to 26 months after an episode of acute Q-fever. The study population consisted of all 870 acute Q-fever patients, notified by the MHS 'Hart voor Brabant' and 'Brabant Zuid-Oost' with a first day of illness in 2007 or 2008. The MHS 'Hart voor Brabant' sent patients notified in 2007 a questionnaire in February 2009 (13–26 months after the onset of acute Q-fever) while this was one year after onset of illness for those notified in 2008. The response rate was 64% (n=556).

What this study adds

- After acute Q-fever, 40% of the gainfully employed were longer than one month absent from work.
- After 12 to 26 months: 9% of those that resumed work were unable to function at pre Q-fever levels, mainly due to fatigue and concentration problems.
- Almost a third of participants did not fully resume daily activities.
- After 12 to 26 months, 40% of participants reported perceived Q-fever related health complaints namely: fatigue 20%, difficulty concentrating 10%, muscle pain 9%, and nighttime sweating 8%.

Recommendations as a consequence of this study

Occupational health professionals, GPs, medical specialists and policy makers need to be aware, informed and instructed on how to deal with these long-term personal and societal (including work) consequences.

Chapter 7, The health status of Q-fever patients after long-term follow-up

Previous knowledge on this subject

Dutch studies often used the validated Nijmegen Clinical Screening Instrument (NCSI) to assess the sub-domains of the health status [14]. Fatigue is a separate sub-domain of this instrument. Several studies reported on prolonged fatigue after acute Q-fever [15-25].

The aim of the study and what was examined

The aim of this study was to provide a detailed assessment of the health status of notified Q-fever patients 12 to 26 months after the onset of illness in 2007 or 2008. This was in order to assist clinicians and patients to better understand the natural course and predictors of an affected health status after acute Q-fever.

The study population, method and response rate are described in **Chapter 6**. The health status and its sub-domains were assessed with the NCSI. Control groups were healthy individuals (n= 65) and Chronic Obstructive Pulmonary Disease patients (COPD) (n= 128).

What this study adds

- 12 to 26 month after onset of illness 7 of 8 NCSI sub-domains of acute and notified Q-fever patients were impaired in comparison to healthy controls.
- Almost 60% of patients reported abnormal fatigue of which 44% was severe.
- The general quality of life was in 45% of cases severely affected.
- Hospitalisation in the acute phase was significantly related to abnormal long-term behavioural impairment, health related quality of life and subjective symptoms.

Recommendations as a consequence of this study

- Inform medical doctors of these detrimental long-term outcomes to enable them to understand and support these patients and refer them to specialist care e.g. a Q-fever expertise centre.
- Develop treatment guidelines for affected patients, GPs and medical specialists.
- Policy makers need to take the long-term burden of infectious diseases into account, when considering measures to control outbreaks.

Chapter 8, The health status of a village population, seven years after a major Q-fever outbreak

Previous knowledge on this subject

From 2010 onwards, information on the long-term health status post Q-fever, assessed with the NCSI, became available from several Dutch studies [22-26]. One year after onset of illness 74% of patients (n=54) reported abnormal fatigue [22].

Seven years after the outbreak started the MHS Hart voor Brabant continued to receive questions from occupational health physicians, GPs, medical specialists and patients regarding the long-term post Q-fever impact on the health status and particular fatigue.

The aim of the study and what was examined

The aim of the 'Q-Herpen-II' study was to assess the presence of *C. burnetii* antibodies in relation to the health status with an emphasis on fatigue. All 2,161 adult inhabitants (≥18 years of age) of the village Herpen (postal code 5373) were invited to fill in a questionnaire including the NCSI and donate blood in January or March 2014. A *C. burnetii* IFA IgG phase I or II titre ≥1:64 was considered positive. The response rate was 71% (1,534/2,161).

What this study adds

- Seven years after the start of the outbreak there was no significant difference in fatigue levels between participants with and without *C. burnetii* antibodies.
- Regardless of the IFA status 38% of participants reported fatigue including 23% with severe fatigue. The IFA status was not an independent risk factor for fatigue.
- Seven years after symptomatic acute Q-fever followed by a national notification [27], 63% (n=31/49) of participants reported fatigue including 47% severe fatigue.
- After a mild or asymptomatic infection that had not been noticed by the participant nor fulfilled the notification criteria [27], 33% (n=150/451) reported fatigue including 20% severe fatigue.
- Fatigue after a *C. burnetii* infection seemed to occur primarily in the group with symptomatic acute Q-fever who as a result fulfilled the national notification criteria [27].
- Knowledge of or belief in a previous infection did not influence the level of fatigue.
- There was no correlation between the *C. burnetii* IFA titre and the level of fatigue.

Recommendations as a consequence of this study

- One ought to be cautious to attribute fatigue to a *C. burnetii* infection. Other morbidities that could cause fatigue should be-as far as possible- excluded first.
- Inquire or check the patients file for the severity of the initial infection.

- Aim to identify in future research what pathogenic mechanisms determine the long-term differences in fatigue between initially symptomatic (notified) and mild or asymptomatic *C. burnetii* infections.

Chapter 9, Fatigue following acute Q-fever: a systematic literature review

Previous knowledge on this subject

Post Infection Fatigue Syndromes (PIFS) [16, 17] can occur after infections [18] such as *Borrelia burgdorferi* [19], *Legionella pneumophila* [24], *Epstein Barr* and *Ross River virus* [18].

In Australia Q- fever fatigue syndrome (QFS) is the most common chronic sequel of acute Q-fever and affects 10-15% of patients [20]. Protracted fatigue after acute Q-fever can last 10 [17, 21] to 20 years [28] and can present with accompanying symptoms that resemble [16] the Chronic Fatigue Syndrome (CFS).

Hypotheses on aetiology were contradictory [29] and varied from altered cytokine production [30], development of symptoms determined by host and genetic factors [30-32], to the perpetuation of symptoms due to psychogenic factors and behaviour [33]. Opinions on possible treatment of QFS varied [34-36], and questions existted regarding prevention and prognosis.

The aim of the study and what was examined

Recurrent questions regarding the definition, background/description, aetiology, prognosis, prevention and treatment of fatigue after a *C. burnetii* infection led to a systematic review (SR). Through a SR all relevant available literature on these subjects searched with PubMed, Embase and PsycInfo up to 26 May 2015 was assessed, resulting in the inclusion of 61 articles.

What this study adds

- A chronological overview of available literature on fatigue after a *C. burnetii* infection up to 26 May 2015, organised in definition, aetiology, background, prognosis and treatment.
- Uniform international definitions of long-term post infection fatigue or QFS were unavailable, and assessment/measurement tools differed between studies, which affects the interpretation of diagnosis, prevalence, aetiology, prognosis and choice of treatment.
- Only the Dutch QFS guideline provided a step by step plan to diagnose QFS.
- Commonly reported symptoms accompanying fatigue following *C. burnetii* infection were musculoskeletal complaints, neurocognitive symptoms, sleeping problems, headaches, blurred vision, increased (night) sweating, respiratory complaints, and mood disorders.
- Fatigue following acute Q-fever carries a large burden of disease and has a major negative impact on the health status of patients with significant economic implications. The majority of patients returned to work within the first 12 months after acute Q-fever, although up to 20% reported reduced work participation.

- Aetiology: the role of genetic variations in host immune responses in QFS was contradictory and might result from individual immune responses to *C. burnetii* rather than from a genetic signature. Cytokine dysregulation mediating symptoms in QFS may originate from immunomodulatory complexes of non-viable undegraded *C. burnetii* DNA or its antigens but results were contradictory.
- A predictor for post-infective fatigue, including QFS: was the severity of the acute Q-fever episode. Neither psychological nor microbial factors were predictors.
- Treatment: no randomized controlled trials (RCT's) were performed, and available data are scarce and inconsistent. The Dutch QFS guideline suggests that Cognitive Behavioural Treatment (CBT) and Graded Exercise Therapy (GET) might reduce fatigue in patients with QFS although evidence is lacking.

Recommendations as a consequence of this study

- International consensus is needed to determine the definition of PIFS and the use of a tool to measure it. Not only Q-fever but also other infectious diseases that can lead to this syndrome should be considered. In the absence of such international consensus the most recent detailed description and diagnosis formulated in the Dutch QFS guideline [36] would suffice.
- Only prospective, clinical studies and treatment trials such as the Qure study [37] might answer questions regarding definition, prognosis, treatment and outcome of fatigue after an infection with *C. burnetii.*
- Aim to identify in future research the pathogenic mechanism that determines the difference in fatigue outcome between symptomatic and mild or asymptomatic *C. burnetii* infections.

Discussion part II

It is important to use a validated and uniform tool to assess post-infective fatigue, including QFS. Interestingly when patients were asked if they were fatigued, 8% answered positively (Chapter 6). When assessed with the NCSI the same study population of acute Q-fever patients reported 60% abnormal fatigue of which 44% was severe (Chapter 7). This large difference emphasises the importance of a standardised tool for any comparison.

In future studies, control groups should be appropriate and serologically tested for *C. burnetii* antibodies. Initially our control groups consisted of healthy controls (Chapter 7) that had not visited a specialist 6 months prior to recruitment and were thus healthier than the general population. The other control group (Chapter 7) consisted of COPD patients. Patients had suffered an episode of acute Q-fever followed by registration by the MHS and national notification. The two control groups were not serologically tested for *C. burnetii* antibodies. The population study (Chapter 8) is however a realistic representation of the

population, furthermore every participant was serologically tested for *C. burnetii* antibodies. This study provided the unique opportunity to compare those with past acute Q-fever, mild, unnoticed or asymptomatic *C. burnetii* infections, and seronegatives which led to unexpected but more realistic findings. Our finding that the health status and level of fatigue at group level was similar for seropositives and seronegatives was comparable with a small study of Limonard *et al.* [23]. Limonard described that the health status of *C. burnetii* seropositive (n=11) and seronegative controls (n=23) was similar. Our large study had enough power to corroborate this point. It also confirmed previous observations that fatigue usually follows acute Q-fever and rarely if ever subclinical infection [20].

After the results from the studies described in Chapters 6 and 7 were released the MHS Hart voor Brabant urged for a standardised approach of those who suffered long-term fatigue after acute Q-fever. This led to the multidisciplinary QFS guideline [36]. The patient organization Q-uestion was represented in the working group. This led to collaboration of the patient organisation in design of the Q-Herpen II Population study and in dispersal of the outcomes in laymen's terms.

The full impact of the outbreak including work related factors will be further investigated in the study "ImpaQt" [38], a meta- analysis that will amongst other studies include data from three of our studies (Chapters 6,7 and 8).

Conclusions

Through a series of studies we answered questions regarding screening for chronic Q-fever and assessed the health status including fatigue after a *C. burnetii* infection.

The main lessons learnt regarding serological screening for chronic Q-fever are:

- Following diagnosis, serological follow-up has a high compliance when organised centrally. When informed as to the why and timing of the follow-up, patients are perfectly able to make a choice in their own best interest by presenting for screening. Follow-up dependent on the initiative of the treating medical doctor is inadequate.
- Serological follow-up at 3,6,9 and 12 months is indicated for groups at high risk for a chronic infection while screening once within 12 months might be sufficient for others.
- General population screening for chronic Q-fever years after an outbreak in a high incidence area, has a low yield and is not advisable. Instead, known cardiovascular risk groups for chronic Q-fever should be screened and vaccinated if applicable as soon as there is an outbreak in their residential area.

The main lessons learnt regarding the health status are:

- 12 to 26 months after acute Q-fever patients had an affected health status, especially fatigue. This was reflected in both a reduced ability to work and performance of daily

activities. As the outbreak was very large this had socio-economic implications for affected individuals, their families and communities.

- Seven years after the start of the outbreak, the IFA status, at population level, was not an independent risk factor for an impaired health status or fatigue. The long-term difference in health status between symptomatic, mild and asymptomatic casus regarding fatigue is noticeable. Although this seemed a difficult message to convey, it was well received by the general public.
- We found no unanimous answers to questions regarding the definition, diagnosis, aetiology, prognosis and best treatment of fatigue after a Q-fever infection. The main reason being differences in definitions and tools used to assess the level of fatigue.

Although the Q-fever outbreak stopped, the long-term sequels of *C. burnetii* infections still require attention. It is conceivable that new outbreaks will occur in other countries. Lessons learnt from our studies may benefit both outbreak management and the after care of patients.

It is essential to engage patients and patient organisations at an early stage during an outbreak and be transparent, regardless of the content of the message. This builds trust and empowers patients. This is especially important in rural and semi-rural areas with intensive animal husbandry activities and fear of the general public of yet another outbreak of a zoonosis.

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SAMENVATTENDE DISCUSSIE

Hoofdstuk 2 is descriptief, beschrijft de 2007 - 2010 Q-koorts uitbraak en geeft algemene informatie over de diagnose van *C. burnetii*, gevolgen van infectie en veterinaire maatregelen.

Deel I. Serologische screening voor chronische Q-koorts.

Hoofdstuk 3, Grote regionale verschillen in serologische follow-up van patiënten met Q-koorts in Nederland

Kennis over dit onderwerp

Ongeveer 2% [1] van patiënten met acute Q-koorts ontwikkelt chronische Q-koorts. Serologische follow-up van patiënten met acute Q-koorts is essentieel voor het herkennen en tijdig behandelen van chronische Q-koorts [2-4]. Tijdens de Nederlandse Q-koorts uitbraak werd geen nationale richtlijn voor serologische follow-up van acute Q-koorts opgesteld.

De gemeenschappelijke gezondheidsdienst (GGD) Hart voor Brabant, ontving informatie van patiënten en gezondheidszorg personeel dat niet alle Q-koorts patiënten serologische follow-up ontvingen en dat er mogelijk regionale verschillen waren in de follow-up procedure.

Het doel van het onderzoek en wat onderzocht werd

Het doel van dit onderzoek was nagaan in welke mate patiënten met acute Q-koorts serologische follow-up kregen en regionale verschillen in de organisatie van follow-up, kennis en gedrag van behandelaars met betrekking tot serologische follow-up, inventariseren.

Tijdens dit onderzoek gebruikten wij data van 3.198 patiënten met een acute infectie tussen 2007 en 2009 gediagnosticeerd, door een van de drie Laboratoria Medische Microbiologie (LMM) in Noord-Brabant. Eén LMM bood patiënten actieve follow-up, door patiënten een herinnering voor bloedafname te sturen. Terwijl de andere twee LMM alleen een serologisch test uitvoerden, na aanvraag van een arts. Het follow-up percentage van de twee systemen werd vergeleken. De kennis van serologische follow-up van Q-koorts van 209/501 huisartsen (HA) en 32/112 medische specialisten werd onderzocht d.m.v. een vragenlijst.

Wat deze studie toevoegt

- De serologische follow-up van patiënten met acute Q-koorts toonde een grote variatie tussen de drie laboratoria en liep uiteen van 25% tot 95% [5].
- Tot 95% van patiënten, volgde een actieve oproep voor serologisch testen op.
- Wanneer de oproep alleen afhing van de HA/specialist, ontving 25% van patiënten serologische follow-up.
- Twee derde van HA en specialisten identificeerde risicogroepen voor chronische Q-koorts correct.

- 35% van de HA en 22% van de medische specialisten vroegen nooit serologische follow-up aan.
- 63% van de HA en 45% van de medische specialisten namen aan dat serologische follow-up na acute Q-koorts georganiseerd werd door een GGD of een LMM.

Aanbevelingen als gevolg van deze studie

- Een actieve oproep van patiënten door een LMM resulteert in het hoogste serologische follow-up percentage voor Q-koorts. Overweeg actieve oproep ook voor andere infectieziekten waarbij serologische follow-up nodig is. Bespreek met laboratoria, behandelaars, patiëntenorganisaties of patiëntengroepen welk oproepsysteem het beste kan werken in een gegeven situatie.
- Geef iedere patiënt met acute Q-koorts een folder met uitleg over het belang van serologische follow-up en laboratoriumformulieren met follow-up data. De behandelaar/assistent kan dit laatste uitvoeren.
- Includeer aanbevelingen m.b.t. serologische follow-up in een nationale richtlijn.

Hoofdstuk 4, Strategieën voor vroegsignalering van chronisch Q-koorts; een systematisch literatuur onderzoek

Kennis over dit onderwerp

De internationale literatuur suggereerde minimaal twee serologische testen (drie en zes maanden) het eerste jaar na acute Q-koorts [3,4,6]. In 2008 adviseerden Nederlandse auteurs [7] om drie, zes, en twaalf maanden na de diagnose te testen. Drie jaar later, was de suggestie om voor serologische follow-up laag en hoog risico patiënten voor chronische Q-koorts te onderscheiden [8]. De eerste groep éénmalig te testen na negen maanden en de tweede groep na drie, zes, negen en twaalf maanden [8]. Er zijn studies met aanbevelingen over follow-up en screeningsstrategieën voor de vroege signalering van chronische Q-koorts maar geen internationale richtlijnen.

Het doel van het onderzoek en wat onderzocht werd

Het doel van de studie was de evidentie van verschillende follow-up en screeningsstrategieën voor de vroegsignalering van chronische Q-koorts nagaan. Hierbij werd rekening gehouden met criteria voor een hoog risico voor een chronische infectie, de frequentie en timing, het interval en de duur van follow-up.

Tijdens een systematische literatuur onderzoek werd alle relevante literatuur, beschikbaar via PubMed of Embase tot 17 oktober 2012, doorgenomen. Dit resulteerde in de inclusie van 20 publicaties.

Wat deze studie toevoegt en aanbevelingen

- Een consensus over de definitie van follow-up strategie ontbreekt. De meeste studies suggereerden serologische follow-up van acute Q-koorts patiënten maar informatie over het moment, frequentie en de duur waren inconsistent.
- Alleen acute Q-koorts patiënten met de klinische indicatie van een cardiale klep abnormaliteit behoren echocardiografie te krijgen.
- Geef patiënten na acute Q-koorts met een bekende risicofactor frequente serologische en klinische follow-up. Voor patiënten zonder risicofactor volstaat éénmalige follow-up tijdens het eerste jaar maar wel na drie maanden b.v. 6 of 9 maanden.
- Kom tot nationale en internationale richtlijnen m.b.t. de klinische en serologische follow-up van acute Q-koorts.
- Overweeg in uitbraak situaties serologische screening van hoog risicogroepen op *C. burnetii*.

Hoofdstuk 5, Populatiescreening voor chronische Q-koorts zeven jaar na een grote uitbraak

Kennis over dit onderwerp

In 2007, waren 25% van de onderzochte inwoners van Herpen, het eerste Nederlandse dorp met een Q-koorts uitbraak, seropositief [9]. In de nabijheid van dit dorp waren tussen 2007 en 2010 vier geitenbedrijven *C. burnetii* positief. Hiervan hadden twee bedrijven *C. burnetii* geïnduceerde abortussen in april 2007 en mei 2008. Eén bedrijf lag in het dorp en het verste lag op zes kilometer afstand van het dorpscentrum.

Een immunofluorescentie test (IFA) IgG antibody titer fase I ≥1:1.024 tijdens follow-up is een belangrijke marker voor een chronische infectie [8].

Het doel van het onderzoek en wat onderzocht werd

De serologische *C. burnetii* status van inwoners van Herpen werd zeven jaar na het begin van de uitbraak onderzocht om chronische Q-koorts op te sporen, ook na een asymptomatische infectie. Het doel van dit onderzoek was personen met chronische Q-koorts tijdig behandelen en de noodzaak inschatten van grootschalige screening in andere uitbraakgebieden.

De serologische *C. burnetii* status van 1.517 volwassen bewoners (71% respons) werd nagegaan met de IFA. De IFA afkapwaarde van IgG fase I of II ≥1:64 wees op een doorgemaakte *C. burnetii* infectie. Deelnemers met een IgG fase I ≥1:512 [10] werden beschouwd als risicovol voor chronische Q-koorts. Zij werden voor nader klinisch onderzoek verwezen om deze diagnose al dan niet te sluiten.

Wat deze studie toevoegt

- Bijna 34% (513/1.517) van de deelnemers was zeven jaar na het begin van de uitbraak, *C. burnetii* seropositief.
- 17% van de in 2007 IFA positieve deelnemers seroconverteerden en waren seronegatief in 2014. De inschatting is daarom dat 41% van de deelnemers een *C. burnetii* infectie doormaakten.
- Van zes deelnemers, 1,2% van de seropositieven, was de IgGI titer ≥1:512. Allen waren PCR negatief. Twee van deze deelnemers kregen al eerder de diagnose chronische Q-koorts. De overige vier werden klinisch onderzocht. Eén van hen, een man ouder dan 65 jaar, met een toegenomen erythrocyten sedimentatie snelheid, renale insufficiëntie, diabetes mellitus type 2, en een cardiale ruis, kreeg de diagnose chronische Q-koorts. Anamnestisch had hij geen acute Q-koorts episode doorgemaakt.
- Van de 69 deelnemers die bekend waren met cardiovasculaire risicofactoren, bleken 16 (23%) IFA-positief. Bij drie deelnemers was dit na Q-koorts vaccinatie, terwijl 13 op natuurlijke wijze geïnfecteerd werden. Twee van deze 13 deelnemers (15%) ontwikkelden chronische Q-koorts.
- Het screenen van de algemene volwassen populatie van Herpen, zeven jaar na het begin van de uitbraak, identificeerde één nieuw (1/1.517) geval van chronische Q-koorts.

Aanbevelingen

- Screen patiënten bekend met cardiovasculaire risicofactoren voor chronische Q-koorts, voor *C. burnetii* zodra een uitbraak is vastgesteld en vaccineer deze onbeschermde risicogroep.
- Houdt rekening met seroreversie. Negatieve *C. burnetii* serologie (IFA) sluit een eerdere infectie niet uit. Overweeg dit bij de vaccinatie van hoog risicogroepen.
- Huisartsen in een hoog incidentie gebied dienen zich te realiseren dat chronische Q-koorts zich ook kan ontwikkelen na het doormaken van een asymptomatische *C. burnetii* infectie.
- Algemene populatiescreening voor chronische Q-koorts, zeven jaar na het begin van een uitbraak, lijkt weinig op te leveren.

Discussie deel I.

Het is essentieel dat iedereen met de diagnose acute Q-koorts informatie ontvangt over chronische Q-koorts, het belang van serologische follow-up en deze follow-up krijgt [5], vooral tijdens het eerste jaar na de infectie [10]. Geïnformeerde patiënten kunnen de behandelaar verzoeken om serologische follow-up wanneer deze niet wordt aangeboden. Tijdens de Q-koorts uitbraak in Nederland, bleek dat het serologisch testen van acute Q-koorts patiënten tijdens het eerste jaar, 98% [10] van chronische Q-koorts al opspoorde.

De tijd tussen de ontwikkeling van chronische Q-koorts en de diagnose na een asymptomatische infectie is onbekend. Chronische Q-koorts kan [4,11] jaren na de infectie opgespoord worden wanneer men niet eerder screent. In geval van niet opgespoorde chronische Q-koorts gaat het vaak om aanvankelijk symptomatische patiënten die geen medische hulp zochten of geen follow-up ontvingen. Of personen die een asymptomatische infectie doormaakten. Van alle in de Nederlandse databank geregistreerde gevallen van chronische Q-koorts, kan een minderheid van 38%, zich een episode van acute Q-koorts herinneren [12]. Het opvolgen van asymptomatische of niet gediagnosticeerde *C. burnetii* infecties en of het screenen van personen met een hoog risico voor chronische Q-koorts – om chronische Q koorts vast te stellen, is onmogelijk. Het screenen van een populatie [13], jaren na een grote uitbraak, vergt een forse inspanning en investering en leverde weinig op.

Onmiddellijke openheid over een Q-koorts uitbraak in een regio met informatie aan de bevolking en behandelaars over serologisch screenen en de mogelijke lange termijn complicaties, samen met een actief serologisch follow-up systeem is essentieel om chronische Q-koorts snel te herkennen. Zowel de bevolking als behandelaars zijn zich dan niet alleen bewust van acute Q-koorts tijdens een uitbraak maar ook oplettend in de toekomst met betrekking tot chronische Q-koorts.

De Q-koorts vaccinatiecampagne in 2011, na de uitbraak was beperkt. Het percentage personen met een risicofactor voor chronische Q-koorts dat gevaccineerd werd is laag [4] (zie hoofdstuk 5). Het is onduidelijk of dit een gevolg is van de selectieprocedure van de behandeld arts of dat patiënten zelf besloten zich niet te laten vaccineren. Ook hier is het belangrijk om zowel artsen als de populatie in een uitbraakgebied te informeren zodat personen met een risicofactor hun eigen geïnformeerde keuze kunnen maken.

Deel II. De gezondheidsstatus in het bijzonder vermoeidheid en ziekteverzuim na een *C. burnetii* infectie

Hoofdstuk 6, Zelf gerapporteerd ziekteverzuim en lange termijn symptomen van Q-koorts

Kennis over dit onderwerp

Nationale of internationale studies, over ziekteverzuim en de mogelijkheid tot werken waren in 2009 niet beschikbaar via Pubmed.

De GGD Hart voor Brabant ontving regelmatig vragen van bedrijfsartsen, huisartsen, medische specialisten en patiënten over de impact van Q-koorts op aanhoudende symptomen, in het bijzonder vermoeidheid en consequenties voor werk.

Het doel van het onderzoek en wat onderzocht werd

Het doel was om de frequentie en duur van ziekteverzuim, symptomen en geassocieerde risicofactoren 12 tot 26 maanden na acute Q-koorts, na te gaan. De studiepopulatie bestond

uit alle 870 patiënten met acute Q-koorts en een eerste ziektedag in 2007 or 2008 die gemeld werden door de GGDen 'Hart voor Brabant' and 'Brabant Zuid-Oost'. De GGD 'Hart voor Brabant' stuurde patiënten die in 2007 gemeld werden in februari 2009 een vragenlijst (13–26 maanden na de eerste ziektedag). Voor patiënten die in 2008 gemeld werden, was dit een jaar na aanvang van de symptomen. De respons was 64% (n=556).

Wat deze studie toevoegt

- Na acute Q-koorts, was het ziekteverzuim van 40% van werknemers langer dan één maand.
- Na 12 tot 26 maanden kon 9% van de werknemers die hun werk hervatten niet meer op hetzelfde niveau functioneren als voor acute Q-koorts. Dit was voornamelijk het gevolg van vermoeidheid of concentratieproblemen.
- Bijna één derde van de deelnemers kon de dagelijkse activiteiten niet volledig hervatten.
- Na 12 tot 26 maanden rapporteerden 40% van de deelnemers klachten die zij als een gevolg van de Q-koorts infectie zagen. Deze klachten waren vermoeidheid 20%, concentratieproblemen 10%, spierpijn 9%, en nachtzweten 8%.

Aanbevelingen

- Bedrijfsartsen, huisartsen, medische specialisten en beleidsmakers dienen zich bewust te zijn, geïnformeerd en geïnstrueerd te worden hoe om te gaan met deze lange termijn consequenties voor het individu die ook hun weerslag hebben op maatschappelijk niveau.

Hoofdstuk 7, De gezondheidsstatus van Q-koorts patiënten na lange termijn opvolging

Kennis over dit onderwerp

Nederlandse studies gebruiken vaak het gevalideerde Nijmegen Clinical Screening Instrument (NCSI) om de verschillende subdomeinen van de gezondheidsstatus na te gaan [14]. Vermoeidheid is een apart subdomein van dit instrument. Verschillende internationale studies beschrijven vermoeidheid na acute Q-koorts [15-25].

Het doel van het onderzoek en wat onderzocht werd

Het doel van deze studie is 12 tot 26 maanden na acute Q-koorts de gezondheidsstatus in detail nagaan van de door de GGD in 2007 en 2008 gemelde patiënten. Dit om clinici en patiënten een beter inzicht te geven in het natuurlijk verloop en de voorspellers van de gezondheidsstatus na acute Q-koorts.

De studiepopulatie, methode en respons zijn beschreven in **hoofdstuk 6**. De gezondheidsstatus met de verschillende subdomeinen werden vastgesteld d.m.v. de NCSI. Controlegroepen waren gezonde individuen (n= 65) en patiënten met Chronische Obstructieve Pulmonaire Disease (COPD) (n= 128).

Wat deze studie toevoegt

- 12 tot 26 maanden na aanvang van de acute Q-koorts waren 7 van de 8 subdomeinen van de NCSI significant aangedaan ten opzichte van de gezonde controlegroep.
- Bijna 60% van de Q-koorts patiënten rapporteerde vermoeidheid waarvan 44% ernstige.
- Bij 45% van de Q-koorts patiënten was de algemene kwaliteit van leven ernstig aangedaan.
- Patiënten die tijdens de episode van acute Q-koorts gehospitaliseerd werden, rapporteerden significant vaker lange termijn; gedragsmatige beperkingen, een verminderde gezondheid gerelateerde kwaliteit van leven en subjectieve symptomen.

Aanbevelingen

- Informeer artsen over deze lange termijn gevolgen zodat zij patiënten beter kunnen begrijpen en ondersteunen en hen verwijzen naar specialistische zorg b.v. een Q-koorts expertise centrum.
- Ontwikkel behandelrichtlijnen voor aangedane patiënten en behandelaars.
- Beleidsmakers dienen deze lange termijn ziektelast te overwegen bij besluitvorming over controlemaatregelen bij uitbraken.

Hoofdstuk 8, De gezondheidsstatus van een dorpspopulatie, zeven jaar na een grote Q-koorts uitbraak

Kennis over dit onderwerp

Vanaf 2010, werd informatie van verschillende Nederlandse studies [22-26] over de lange termijn gevolgen van de gezondheidsstatus na acute Q-koorts, gemeten met het NCSI beschikbaar. Eén jaar na het begin van de klachten rapporteerden 74% van deze patiënten (n=54) abnormale vermoeidheid [22].

Zeven jaar na het begin van de uitbraak ontving de GGD Hart voor Brabant nog vragen van bedrijfsartsen, andere medici en patiënten over de lange termijn gevolgen van Q-koorts op de gezondheidsstatus en in het bijzonder vermoeidheid.

Het doel van het onderzoek en wat onderzocht werd

Het doel van de 'Q-Herpen-II' studie was de relatie tussen de aanwezigheid van *C. burnetii* antilichamen en de gezondheidsstatus met de nadruk op vermoeidheid nagaan. Alle 2.161 volwassen inwoners (18 jaar en ouder) van het dorp Herpen (postcode 5373) kregen een uitnodiging voor: het invullen van een vragenlijst, waar de NCSI deel van uit maakte en een bloedafname in januari of maart 2014. Een IFA IgG fase I of II titer ≥1:64 werd gezien als positief. De respons was 71% (1.534/2.161).

Wat deze studie toevoegt

- Zeven jaar na het begin van de uitbraak was er geen significant verschil in de mate van vermoeidheid tussen deelnemers met en zonder *C. burnetii* antilichamen.
- Onafhankelijk van de IFA status rapporteerden 38% van de deelnemers vermoeidheid waarvan 23% ernstige. De IFA status was geen onafhankelijke risicofactor voor vermoeidheid.
- Na het doormaken van symptomatische acute Q-koorts gevolgd door een nationale melding [27] was zeven jaar later 63% (n=31/49) van de deelnemers vermoeid, waarvan 47% ernstig.
- Na een milde of asymptomatische infectie die door de betrokkene niet was opgemerkt en niet voldeed aan de meldingscriteria [27] rapporteerde 33% (n=150/451) vermoeidheidsklachten waarvan 20% ernstige.
- Vermoeidheid na een infectie met *C. burnetii* lijkt zich voornamelijk te beperken tot de groep met symptomatische acute Q-koorts die als gevolg daarvan voldeed aan de nationale meldingscriteria [27].
- Het maakte voor de mate van moeheid niet uit of deelnemers al dan niet op de hoogte waren van hun uitslag of dachten dat ze deze infectie doormaakten.
- De *C. burnetii* IFA titer en de mate van vermoeidheid waren niet gerelateerd.

Aanbevelingen

- Betracht voorzichtigheid bij het verklaren van vermoeidheid door een doorgemaakte *C. burnetii* infectie. Andere morbiditeit die vermoeidheid kan veroorzaken dient (voor zover mogelijk) eerst uitgesloten te worden.
- Vraag of ga in het patiëntendossier na wat de ernst van de aanvankelijke infectie was.
- Ga in toekomstig onderzoek na welk pathogeen mechanisme bepalend is voor het verschil in de lange termijn mate van vermoeidheid tussen symptomatische (genotificeerde) en milde of asymptomatische *C. burnetii* infecties.

Hoofdstuk 9, Vermoeidheid na acute Q-koorts: een systematisch literatuuronderzoek

Kennis over dit onderwerp

Post infectieuze vermoeidheidssyndromen (PIVS) [16,17] kunnen ook ontstaan na andere infecties [18] door bijvoorbeeld *Borrelia burgdorferi* [19], *Legionella pneumophila* [24] *Epstein Barr* en *Ross River virus* [18].

In Australia is het Q-koorts vermoeidheidssyndroom (QVS) het meest voorkomende chronische gevolg van acute Q koorts dat bij 10-15% van patiënten voorkomt [20]. Langdurige vermoeidheid na een acute Q-koorts episode kan 10 [17,21] tot 20 jaar [28] aanhouden en gepaard gaan met symptomen die lijken op het chronische vermoeidheidssyndroom (CVS) [16]. Hypothesen m.b.t. de etiologie [29] waren tegenstrijdig en varieerden van een

verstoorde cytokine productie [30], ontwikkeling van symptomen bepaalt door gastheer en genetische factoren [30-32], tot het in standhouden van klachten door psychogene factoren en gedrag [33]. Meningen over de mogelijke behandeling van QVS verschilden [34-36]. Daarnaast bestonden er vragen over preventie en prognose.

Het doel van het onderzoek en wat onderzocht werd

Terugkerende vragen over de definitie, achtergrond/beschrijving, etiologie, prognoses, preventie en behandeling van vermoeidheid na een *C. burnetii* infectie resulteerden in een systematisch literatuuronderzoek. Alle relevante beschikbare literatuur over deze onderwerpen tot 26 mei 2015 werd gezocht met behulp van PubMed, Embase and PsycInfo en resulteerde in de inclusie van 61 artikelen.

Wat deze studie toevoegt

- Een chronologisch overzicht van alle beschikbare literatuur tot 26 mei 2015, over vermoeidheid na infectie met *C. burnetii*, georganiseerd in de onderwerpen definitie, etiologie, achtergrond, prognose en behandeling.
- Een uniforme internationale definitie van lange termijn post infectieuze vermoeidheid (PIV) of QVS was niet beschikbaar. Doordat de meetinstrumenten en methoden verschilden tussen studies, beïnvloedde dit de interpretatie van de diagnosis, prevalentie, etiologie, prognoses en behandelkeuze.
- De Nederlandse QVS richtlijn was het enige document met een stappenplan voor de diagnose QVS.
- Dikwijls gerapporteerde klachten die samengaan met vermoeidheid na een Q-koorts infectie waren: musculoskeletaire klachten, neurocognitieve symptomen, slaapproblemen, hoofdpijn, wazig zicht, toegenomen (nacht) zweten, respiratoire klachten, en stemmingsstoornissen.
- Vermoeidheid na acute Q-koorts heeft een grote ziektelast en negatieve impact op de gezondheidsstatus van patiënten en hierdoor economische implicaties. De meerderheid van patiënten werkten weer binnen 12 maanden na acute Q-koorts, maar bijna 20% rapporteerde afgenomen werk participatie.
- Etiologie: de rol van genetische variatie in de gastheer immuun-reactie bij QVS was tegenstrijdig en kan een gevolg zijn van individuele immuunreacties op *C. burnetii* in plaats van genetische kenmerken. Cytokine disregulatie die symptomen in QVS beïnvloeden kunnen een gevolg zijn van immunomodulatoire complexen van niet levend niet afgebroken *C. burnetii* DNA of antigenen, maar resultaten waren tegenstrijdig.
- Een voorspeller voor PIVS inclusief QVS: was de ernst van de acute Q-koorts. Psychologische of microbiologische factoren waren geen voorspellers.

- Behandeling: gerandomiseerd vergelijkende onderzoeken (RCT's) werden niet uitgevoerd, de weinige beschikbare data waren inconsistent. De Nederlandse QVS richtlijn suggereert dat Cognitieve Gedrags Therapie (CGT) en Graded Exercise Therapy (GET) vermoeidheid in patiënten met QVS kunnen reduceren maar bewijs hiervoor ontbreekt.

Aanbevelingen

- Een internationale consensus is nodig voor het vaststellen van de definitie PIVS evenals uniforme instrumenten. Behalve Q-koorts moet men rekening houden met andere infectieziekten die kunnen lijden tot dit syndroom. Zolang een dergelijke internationale consensus ontbreekt, geeft de Nederlandse QVS richtlijn [36] de meest recente gedetailleerde descriptie en diagnose en is als zodanig bruikbaar.
- Alleen prospectieve, klinische studies en behandel trials zoals de Qure-studie [37] kunnen mogelijk antwoord geven op vragen m.b.t. de definitie, prognose, behandeling en de gevolgen voor vermoeidheid na een *C. burnetii* infectie.
- Toekomstig onderzoek dient het pathogene mechanisme dat een rol speelt in de mate van vermoeidheid tussen symptomatische en milde of asymptomatische *C. burnetii* infecties na te gaan.

Discussie deel II

Het gebruik van een gevalideerd uniform instrument om PIVS, inclusief QFS na te gaan is essentieel. Acht procent van patiënten gaf aan dat zij vermoeid waren als deze vraag werd gesteld (Hoofdstuk 6). Dezelfde studiepopulatie rapporteerde 60% abnormale vermoeidheid waarvan 44% ernstig bij invullen van de NCSI (Hoofdstuk7). Dit grote verschil illustreert en benadrukt het belang van het gebruik van een gestandaardiseerd instrument voor enige vergelijking.

In toekomstige studies, hoort de controlegroep zorgvuldig gekozen en serologisch getest te worden op *C. burnetii* antilichamen. Aanvankelijk bestond de controlegroep uit gezonde personen (Hoofdstuk 7) die de afgelopen maanden geen specialist bezochten en daarom gezonder waren dan de algemene populatie. De andere controlegroep bestond uit personen met COPD (Hoofdstuk 7). Patiënten hadden acute Q-koorts doorgemaakt, waren geregistreerd door de GGD en nationaal gemeld. De twee controlegroepen werden niet serologisch getest op aanwezigheid van *C. burnetii* antilichamen. De populatiestudie (Hoofdstuk 8) is wel een realistische weergave van de volwassen populatie en iedere deelnemer werd serologische getest op *C. burnetii* antilichamen. Deze studie bood de unieke kans om acute Q-koorts, milde, onopgemerkte en asymptomatische *C. burnetii* infecties te vergelijken met seronegatieven, wat resulteerde in onverwachte maar meer realistische bevindingen. De bevinding dat de gezondheidsstatus en de mate van vermoeidheid vergelijkbaar was tussen sero- positieve en negatieve deelnemers kwam overeen met een kleine studie van Limonard

et al. [23]. Limonard beschreef dat de gezondheidsstatus van *C. burnetii* seropositieve (n=11) en negatieve (controles) (n=23) vergelijkbaar was. Onze grote studie (Hoofdstuk 8) had voldoende power om dit punt te confirmeren. Het bevestigde ook de eerdere veronderstellingen dat vermoeidheid in het algemeen ontstaat na acute Q-koorts en zeer zelden na een subklinische infectie [20].

Nadat de resultaten van de studies beschreven in hoofdstuk 6 and 7 openbaar werden drong de GGD Hart voor Brabant aan op een gestandaardiseerde benadering van personen met langdurige vermoeidheid na acute Q-koorts. De multidisciplinaire QVS richtlijn [36] ontstond mede als gevolg hiervan. De patiëntenorganisatie Q-uestion nam actief deel aan de werkgroep van deze richtlijn. Zo ontstond een samenwerking met Q-uestion die o.a. resulteerde in een bijdrage aan de vormgeving van de "Q-Herpen II" populatiestudie en het bekendmaken van de resultaten in lekentaal.

De volle impact van de uitbraak, inclusief werk gerelateerde factoren, zal onderzocht worden in de studie "ImpaQt" [38], een meta-analyse, die naast andere studies ook data van de drie hier beschreven studies in hoofdstukken 6, 7 en 8 includeert.

Conclusies

Via een reeks studies was het mogelijk vragen met betrekking tot het screenen voor chronische Q-koorts en de gezondheidsstatus inclusief vermoeidheid na een infectie met *C. burnetii,* te beantwoorden.

De belangrijkste lessen met betrekking tot serologische screening voor chronische Q-koorts zijn:

- Centraal georganiseerde serologische follow-up heeft een hoge respons. Patiënten die geïnformeerd worden over de redenen en momenten van follow-up zijn goed in staat om een eigen keuze te maken. Dit uit zich in een hoog percentage patiënten dat zich screent. Follow-up wordt onvoldoende geïnitieerd door behandelaars.
- Serologische follow-up op 3, 6, 9 en12 maanden is geïndiceerd voor hoog risicogroepen voor chronische Q-koorts. Eenmalig screenen binnen 12 maanden na de acute infectie kan voldoende zijn voor anderen.
- Een algemene populatiescreening voor chronische Q-koorts, zeven jaar na een uitbraak in een hoog incidentie gebied, levert weinig op en is niet aanbevolen. In plaats hiervan is screenen op *C. burnetii* antilichamen van bekende cardiovasculaire risicogroepen voor chronische Q-koorts een optie. Dit dient te gebeuren zodra er een uitbraak is. Vaccinatie dient zo snel mogelijk uitgevoerd te worden als van toepassing.

De belangrijkste lessen m.b.t. de gezondheidsstatus zijn:

- 12 tot 26 maanden na acute Q-koorts hadden deelnemers een aangedane gezondheidsstatus met vooral vermoeidheid. Zij rapporteerden zowel een afname in de uitvoer van hun werk als hun dagelijkse activiteiten. Omdat de uitbraak groot was had dit socio-economische implicaties voor de betrokken individuen, hun families en gemeenschappen.
- De IFA status was zeven jaar na de uitbraak, op populatie niveau, geen onafhankelijke risicofactor voor een slechtere gezondheidsstatus of vermoeidheid. Met betrekking tot vermoeidheid is het verschil tussen acute Q-koorts, milde en asymptomatische infecties opvallend. Deze schijnbaar moeilijke boodschap werd goed ontvangen door het algemene publiek.
- Eenduidige antwoorden op vragen m.b.t. de definitie, diagnose, etiologie, prognose en de beste behandeling van vermoeidheid na Q-koorts waren niet beschikbaar. De belangrijkste reden was de verschillen in definities en instrumenten die gebruikt werden om de mate van vermoeidheid vast te stellen.

De Q-koorts uitbraak in Nederland is gestopt. Nu vragen vooral de lange termijn complicaties van *C. burnetii* infecties aandacht. Het is goed mogelijk dat nieuwe uitbraken in andere landen ontstaan. Anderen kunnen dan profiteren van de hier geleerde lessen. Dit kan het uitbraakmanagement en de nazorg van patiënten ten goede komen.

Onafhankelijk van de boodschap, is het essentieel om patiënten en patiëntenorganisaties in een vroeg stadium van een uitbraak te betrekken, en transparant te zijn. Zo bouwt men vertrouwen op en geeft patiënten kennis en macht. Dit is bijzonder belangrijk in rurale en semi-rurale gebieden met intensieve veehouderij en de angst van de bevolking voor een volgende zoönose uitbraak.

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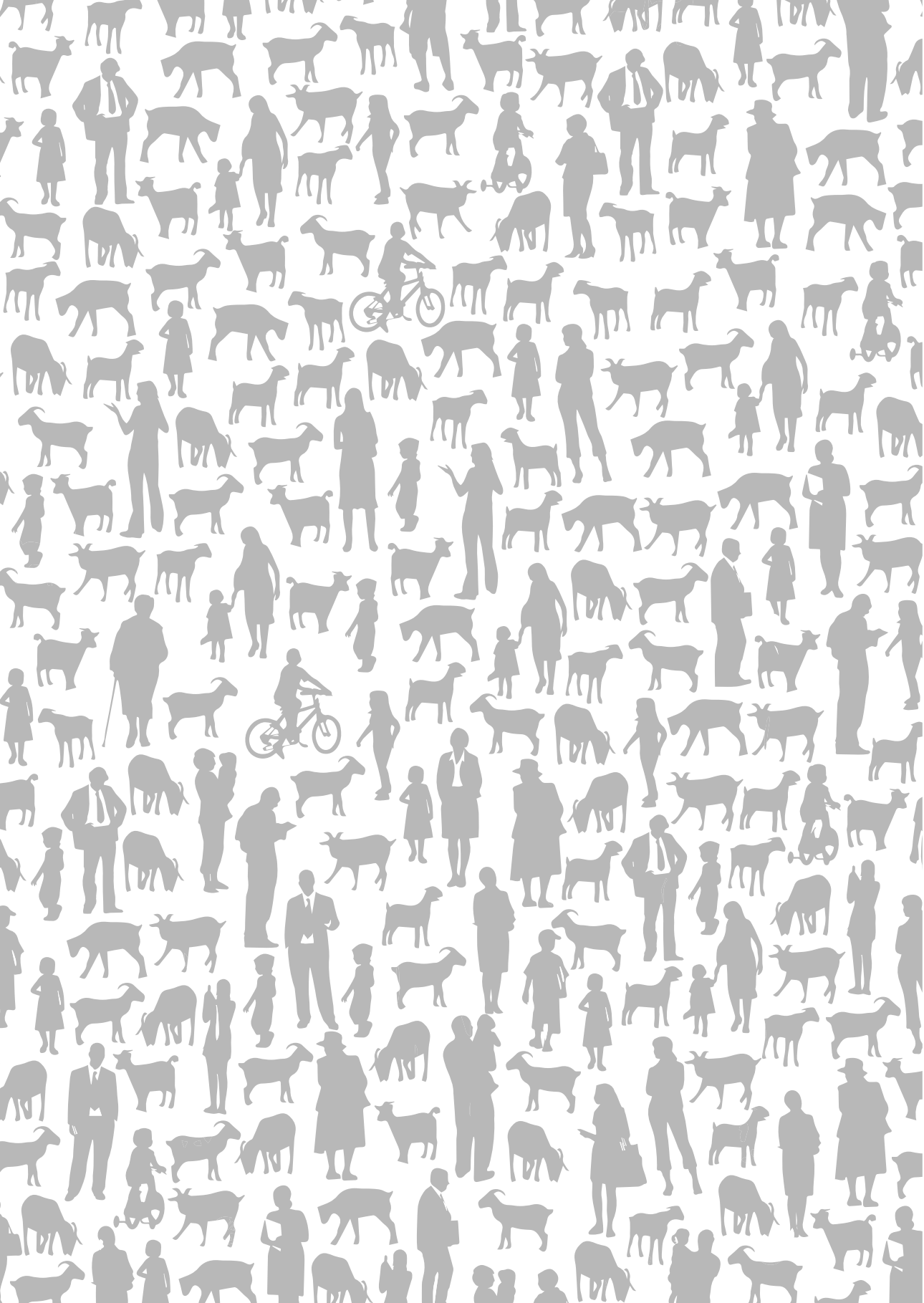

CHAPTER 11

DANKWOORD
ABOUT THE AUTHOR
OTHER PUBLICATIONS

DANKWOORD

Mooi dat wetenschappelijk onderzoek deel uitmaakt van de opleiding arts maatschappij en gezondheid. Van idee tot publiceerbaar artikel in 56 dagen, is een goede stok achter de deur.

Het onderzoek begon als een economische studie. Johan Polder[1], jij gaf aan: “als je denkt dat je het kan - doen!”. Onze gesprekken inspireerden mij. Je maakte altijd tijd vrij om mij een zetje te geven. Juriaan Prins[2], onvermoeibaar stopte je veel uren in de kostenstudie. Een openbaring al die berekeningen. Dank voor alle inzet en uitleg.

Hans Bor[3], vanaf het begin was je betrokken bij mijn onderzoeken. Jouw uitleg en advies over datamanagement en analyse waren een ontdekkingsreis in de wereld van de biostatistiek, aan de hand van een geduldige bescheiden leermeester. Jij gaf telkens aan: “maak er een promotietraject van“. Hans, dank voor dit alles, dit manuscript is het resultaat!

Van de GGD en het team infectieziektebestrijding dank ik een ieder die mijn promotietraject mogelijk maakte, faciliteerde en/of mij een warm hart toedroeg. Jos van der Sande, jij gaf mij de ruimte te promoveren en streek de kreukels glad. Jou dank ik in het bijzonder voor jouw benaderbaarheid, spitsvondigheid en vertrouwen in mij. Clementine Wijkmans, jij vertegenwoordigde de GGD Hart voor Brabant en het onderzoek tijdens vele overleggen en uren.

Twee promotoren. Wat een luxe! Koos van der Velden, je laveerde succesvol tussen de klippen door en glimlachte om en tegen de beren op de weg. Roel Coutinho, wereldreiziger met een overvolle agenda. En toch die snelle, vakkundige reactie. Commentaar, recht voor z’n raap altijd open voor discussie. Wat bevrijdend! Wim van de Hoek, steeds wist je tekst waar ik op vastliep vlot te trekken. Wim, ik ben dankbaar dat ik op jouw Q-koorts kennis en netwerk mocht mee liften. De promotie overleggen gaven mij nieuwe inzichten en de impuls om door te zetten. Deze discussies, het relativeren en de dosis humor mis ik.

Malou, Paula, Mandy, Anne, Zindia, Jelle en Karen, als stagiaires maakten jullie bijdragen deze onderzoeken mogelijk. De samenwerking was fijn en ook voor mij leerzaam.

Lieke Wielders en Joris van Loenhout, fijn om ad hoc met jullie van gedachten te wisselen over onderzoeke. Dank voor alle steun en advies tijdens dit hele promotieproces.

De lijst van medeauteurs van deze multidisciplinaire onderzoeken is lang. De samenwerking met ieder van jullie was voor mij een leerzaam voorrecht. Peter Schneeberger[5], omdat je eind of medeauteur van op één na alle artikelen in dit proefschrift noem ik jou als enige apart.

[1]Gezondheidseconoom RIVM en Tranzo, [2]Econometrist bij Sociaal Economisch Onderzoek en nu het UWV, [3]Biostatisticus bij de academische werkplaats AMPHI, [4]toenmalig hoofd team algemene gezondheidszorg GGD Hart voor Brabant nu GGD Nederland, [5]arts-medisch microbioloog in het Jeroen Bosch Ziekenhuis.

Peter, dank dat je jouw aanstekelijke enthousiasme, onderzoeksideeën en enorme vakkennis deelde. Jouw commentaar was wervelend snel, tussen drie telefoontjes door, inspirerend, soms cryptisch en stof tot nadenken.

De patiëntenvereniging Q-uestion was toenemend betrokken bij de onderzoeken. Van concept idee tot de communicatie van resultaten aan deelnemers. Michel van de Bergh, Nelleke Maathuis en Ria van Son, jullie vragen, en vertaling naar onderzoeksdeelnemers waren een essentiële bijdrage. Dank voor jullie gedreven inzet.

Wat mooi de optimale samenwerking van zoveel vrijwilligers van vele organisaties bij de uitvoer van Q-Herpen-II in 2014. Het voelde voor mij en ik hoop ook voor jullie als een feestje....

Dank aan alle studiedeelnemers. Dankzij jullie ingevulde vragenlijsten (soms bijna boekwerken) en soms bloeddonaties werden deze onderzoeken mogelijk.

Koos Jaap van Zwieten[6] toen de deuren van de Radboud Universiteit Nijmegen (RU) voor mij, een vierdejaars student geneeskunde uit Suriname in 1984 dicht bleven (behalve voor het eerste studiejaar) vond jij een ingang bij de Universiteit Leuven. Daar ben ik jou altijd dankbaar voor gebleven. Ik nam mij in 1984 voor nooit meer voet in de RU te zetten. Het is daarom bijzonder dat ik juist hier promoveer.

Tijdens dit promotietraject kon ik dankzij AMPHI niet om de RU heen, dat een warm nest bleek. Dank aan een ieder die hier aan bijdroeg.

Het thuisfront moest de afgelopen jaren afzien. Zeker als moeders oa weer geen boodschappen deed, niet kookte, geen tijd had en laat thuiskwam. Benjamin, je moest het maar rechtbreien. Gelukkig stelde je grenzen-"enough time on the confuser @£&!". Juist nu "het" af is en ik er weer helemaal "ben" vliegen jullie, Alia en Savana uit. Ik kan deze jaren niet inhalen maar weet dat jullie voor mij altijd op de eerste plaats staan.

[6]*Emeritus professor Geneeskunde en Levenswetenschappen, Universiteit van Hasselt.*

ABOUT THE AUTHOR

Gabriella Morroy commenced her study of Medicine in 1979 in Surinam, South America. The military coup in 1982 led to the closure of the University in Surinam and an exodus of students. Gabriella travelled to Europe in 1983. In 1988 she obtained her medical diploma from the Catholic University of Leuven, Belgium after her last internship at the Department of Infectious Diseases in Avicenne Hospital, in Rabat, Morocco.

After completing her medical studies, Gabriella worked for six months at the Department of Infectious Diseases at the Municipal Health Service (MHS) in Amsterdam, and a similar period at the National Institute for Public Health and the Environment (RIVM). Gabriella completed eight missions with Médecins Sans Frontières (MSF) France and Holland in Africa and the Middle East. Tasks ranged from curative care, to the training of Community Health Workers, Water and Sanitation Officers and Traditional Midwives; to the coordination of large vaccination campaigns and the management of refugee camps, to the rehabilitation of hospitals and outpatient services.

In 1991 Gabriella obtained her Diploma in Tropical Medicine and Hygiene from the Institute of Tropical Medicine in Liverpool. From 1992 to 1996 Gabriella worked as the country representative for the Tropical Institute of Antwerp on a Sexually Transmitted Infection Intervention Research Programme with the WHO Collaborative group in Nairobi, Kenya. From 1997 onwards Gabriella worked as a Medical Consultant in East Africa and was a co-founder and Community Health Director of Wildlife Works, Kenya http://www.wildlifeworks.com/.

In 2001, Gabriella moved with her partner and two daughters from Kenya to the Netherlands. Initially Gabriella worked at the MHS Noord West Veluwe in Harderwijk, fulfilling a wide range of duties from Social Medical Advice, to Environmental Health and Infectious Diseases. From 2003 onwards she worked at the Department of Infectious Diseases of the MHS Hart voor Brabant in 's-Hertogenbosch. In 2010 Gabriella won the Motivation Prize for Original and Applied Research awarded by the National Institute of Public Health (NSPOH) and became registered as a Medical Consultant Communicable Disease Control. Since mid-2012 she combines work at the MHS with a part time PhD position at the Academic Collaborative Centre (AMPHI) at the Radboud University, Nijmegen.

Gabriella is a member of the Dutch board of Infectious Diseases (NVIB) and secretary of its Education Commission.

Starting in 2011 Gabriella completed three years of the Hatha Yoga teachers' course at Saswitha a Teaching Institute for Yoga and Philosophy (Bilthoven the Netherlands). Since 2012 she is an elected Regional Representative (Region Middle North and East Brabant) of the Diabetes Organisation of the Netherlands (Diabetes Vereniging Nederland).

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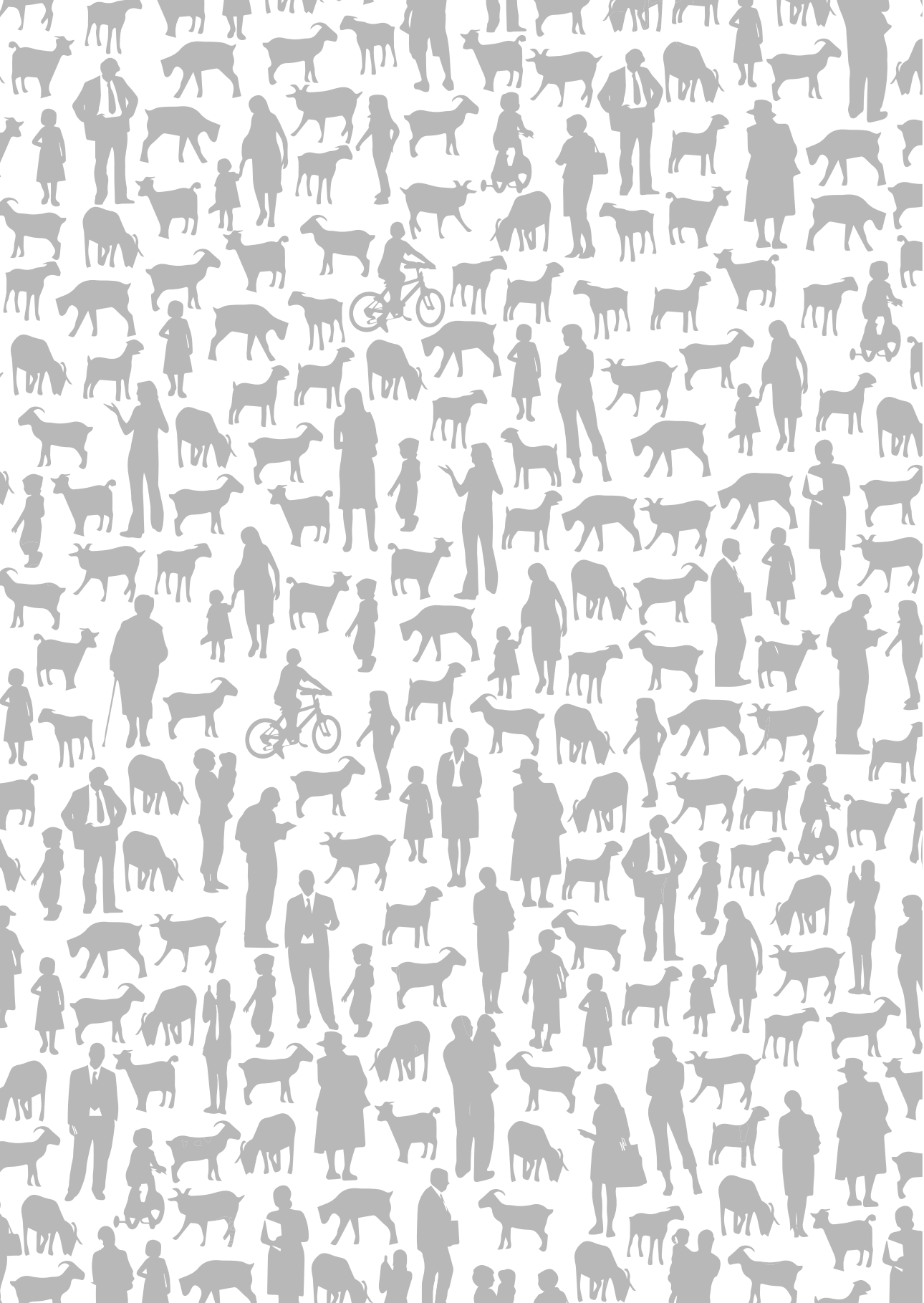

CHAPTER 12

FACT SHEET Q-FEVER

FACT SHEET Q-FEVER

The bacterium *Coxiella burnetii*

In 1937, Derrick first described an outbreak of febrile illness in abattoir workers in Queensland, Australia. The causative pathogen was unknown and he called the symptom complex Q-fever (Q for query). The pathogen was independently isolated by Burnet from a patient via a guinea pig (Australia) and Cox in ticks (USA). Initially named *Rickettsia burnetii* the pathogen was renamed *Coxiella burnetii (C. burnetii)*, in order to honour both Cox and Burnet. Q-fever is a zoonosis caused *by C. burnetii* a Gram negative obligate intracellular highly resistant bacterium, with a worldwide occurrence, except New Zealand. Domestic ruminants are the main reservoir, although rodents, birds and arthropods can also be infected.

Incubation period

The incubation period varies from two to 48 days but is on average 14 to 24 days.

Transmission

Infection of humans occurs mainly after inhalation of contaminated aerosols. During the Dutch outbreak the risk of infection was increased up to 5 km around goat farms that had experienced abortion storms due to *C burnetii*. *C. burnetii* is highly infectious as one organism can cause infection.

Pathogenesis

The inhaled bacteriae are phagocytised by alveolar macrophages in the lungs. Infected macrophages transport *C. burnetii* through the blood stream. Cellular and humoral immunological responses are both involved in the defence.

Clinical expression

Initial infection

The majority approx. 60% of infected individuals are asymptomatic. The clinical manifestations of the 40% symptomatic individuals vary from mild flu like symptoms with fever and headache to more severe manifestations in the remaining 20% with atypical pneumonia. Peri- and myo carditis, meningitis and meningo encephalitis, disorientation, vascular and osteoarticular infections are among the many different manifestations. In the Netherlands, pneumonia was a common presentation of acute Q-fever while hepatitis was rarely observed. In general the infection is self-limiting after one to two weeks.

Long-term sequels

1. Chronic Q-fever

After a symptomatic or asymptomatic infection with *C. burnetii* the immune system might be unable to clear the infection. The infection might flare up and cause a chronic infection. Chronic Q-fever develops in approximately 2% of Q-fever infections and can be detected months—or even years—after the initial infection, which was either symptomatic or asymptomatic. Risk factors include pre-existing cardiac valvulopathy, vascular graft, aneurysm, immuno-suppression and pregnancy. Chronic Q-fever is the most serious complication of Q-fever and can lead to endocarditis, an infected aneurysm or vascular graft, causing high morbidity and mortality even if optimal and timely treatment is received. Chronic Q-fever is not notifiable, therefore precise numbers are unavailable; however, up to May 2012, 284 patients were voluntarily registered into a database as part of a research project run by the University Medical Center Utrecht. For early detection of chronic Q-fever, patients should have at least one serological examination and a clinical evaluation within one year following the acute infection.

2. Fatigue after Q-fever

Fatigue can persist after Q-fever, accompanied by a host of other a specific symptoms such as headache, disturbed sleep, night sweats, myalgia, arthralgia and blurred vision. Some call this syndrome the Q-fever Fatigue Syndrome (QFS) but there are no uniform diagnostic criteria. Similar post infectious fatigue syndromes (PIFS) are described after other infections for example with River Ross virus, Epstein-Barr virus and Legionella pneumophila. Although the aetiology of QFS remains unknown, factors such as genetic predisposition, the hosts' immune response, the severity of the acute illness and or biopsychology could play a role. Five to ten years after the onset of illness up to 68% of patients report fatigue of which QFS may be up to 42%.

Treatment

The first choice of treatment for acute Q-fever is doxycycline (200mg/day for 14 days), whereas chronic Q-fever needs to be treated with 18-24 months of doxycycline in combination with hydroxychloroquine. The most effective treatment for QFS has not been established.

Diagnosis

During approximately the first two weeks after the onset of illness *C. burnetii* DNA may be detected with a Polymerase Chain Reaction (PCR) test. As the antibody response starts after one to two weeks, the PCR becomes negative and serology is the only way to diagnose infection. Common tests are; the complement fixation test (CFT), the Enzyme-Linked Immunosorbent Assay (ELISA) and the indirect immunofluorescence assay (IFA). The IFA is considered the reference method, with IgG phase II antigen titres larger than IgG phase I during the acute

phase of illness. In early acute sera, IgM phase II titres may be higher and appear even sooner than IgG phase II. In general seroconversion or a fourfold titre increase are diagnostic for recent infections.

Notification and the Q-fever outbreak in the Netherlands

In the Netherlands Q-fever became notifiable in 1975. Annually an average of 17 cases was notified. Notification criteria used at the beginning of the outbreak in 2007 were: a laboratory confirmation and matching clinical symptoms. In July 2008 notification criteria were changed to; the presence of fever, pneumonia or hepatitis plus a laboratory confirmation and notified to the MHS within 90 days following the onset of illness. At least one of the following laboratory criteria also had to be met: an IFA or a Complement Fixation Test (CFT) seroconversion or fourfold or larger *C. burnetii* IgG-antibody titre increase in paired sera (minimally two weeks apart) or presence of IgM-Phase II antibodies or a positive *C. burnetii* PCR (unless the sample is from a patient with chronic Q-fever).

From 2007-2010 the largest described Q-fever outbreak ever took place in the Netherlands. In this period, 4,026 cases were notified. The estimation is that 10 to 12 times more people became infected. These data are based on seroprevalence data and information from the blood bank in a high incidence area. This is not surprising as most infections were asymptomatic and some symptomatic cases might not have been diagnosed or did not fit the notification criteria. See figure 1 for the geographical spread of the outbreak in time and figure 2 for the number of notifications in time.

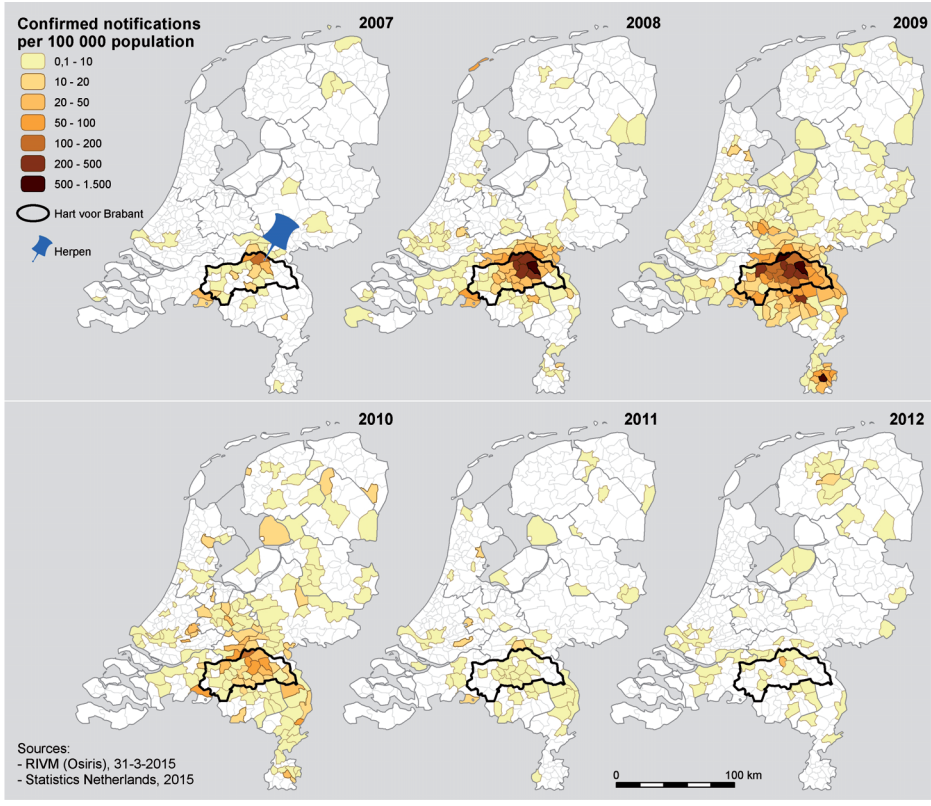

Figure 1.Incidence of notified Q-fever cases per municipality per year.

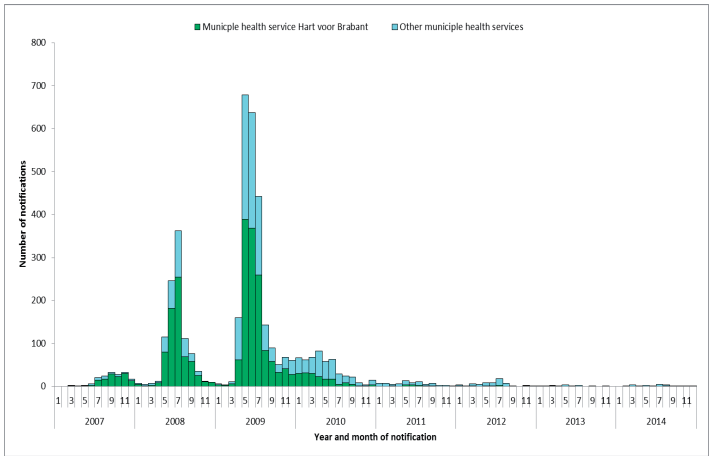

Figure 2.Municipal Health service Q-fever notifications n= 4.220 from 2007 up to 2014 according to month and year of notification, by Hart voor Brabant and other Municipal Health services.